DESCRIPTION

PYRIMIDINE DERIVATIVES AND METHODS OF TREATMENT RELATED TO THE USE THEREOF

Field of the Invention

The present invention relates to compounds which act as antagonists for MCH receptors and to the use of these compounds in pharmaceutical compositions.

Background of the Invention

Melanin Concentrating Hormone (MCH), a cyclic peptide, has been identified as the endogenous ligand of the orphan G-protein coupled receptor SLC-1. See, for example, Shimomura et al., Biochem. Biophys. Res. Commun. 261, 622-26 (1999). Studies have indicated that MCH acts as a neurotransmitter/neuromodulator to alter a number of behavioral responses such as feeding habits. For example, injection of MCH into rats has been reported to increase their consumption of food. Reports indicate that genetically engineered mice which lack MCH show lower body weight and increased metabolism. See Saito et al., TEM, vol. 11, 299 (2000). As such, the literature suggests that discovery of MCH antagonists that interact with SCL-1 expressing cells will be useful in developing obesity treatments. See Shimomura et al., Biochem. Biophys. Res. Commun. 261, 622-26 (1999).

G protein-coupled receptors (GPCRs) share a common structural motif. All these receptors have seven sequences of between 22 to 24 hydrophobic amino acids that form seven alpha helices, each of which spans the membrane. The fourth and fifth transmembrane helices are joined on the extracellular side of the membrane by a strand of amino acids that forms a relatively large loop. Another larger loop, composed primarily of hydrophilic amino acids, joins transmembrane helices five and six on the intracellular side of the membrane. The carboxy terminus of the receptor lies intracellularly, and the amino

terminus lies in the extracellular space. It is thought that the loop joining helices five and six, as well as the carboxy terminus, interact with the G protein. Currently, Gq, Gs, Gi, and Go are G proteins that have been identified as possible proteins that interact with the receptor.

Under physiological conditions, GPCRs exist in the cell membrane in equilibrium between two different states or conformations: an "inactive" state and an "active" state. A receptor in an inactive state is unable to link to the intracellular transduction pathway to produce a biological response. Changing the receptor conformation to the active state allows linkage to the transduction pathway and produces a biological response.

A receptor may be stabilized in an active state by an endogenous ligand or an exogenous agonist ligand. Recent discoveries, including but not exclusively limited to, modifications to the amino acid sequence of the receptor, provide alternative mechanisms other than ligands to stabilize the active state conformation. These approaches effectively stabilize the receptor in an active state by simulating the effect of a ligand binding to the receptor. Stabilization by such ligand-independent approaches is termed "constitutive receptor activation." In contrast, antagonists can competitively bind to the receptor at the same site as agonists, but do not activate the intracellular response initiated by the active form of the receptor, and therefore inhibit the intracellular responses by agonists.

Certain 2-aminoquinazoline derivatives have been reported to be NPY antagonists which are said to be effective in the treatment of disorders and diseases associated with the NPY receptor subtype Y5. See PCT Patent Application 97/20823. Quinazoline derivatives have also been found to be useful by enhancing antitumor activity. See PCT Patent Application 92/07844. And also the quinoline derivatives which have an antagonist activity for MCH receptor are known in these patents, WO03/070244, WO03/105850, WO03/45313, WO03/045920, and WO04/04726.

Recently, our current knowledge of human obesity has advanced dramatically. Previously, obesity was viewed as an oppugnant behavior of inappropriate eating in the setting of appealing foods. Studies of animal models of obesity, biochemical alterations in

both humans and animals, and the complex interactions of psychosocial and cultural factors that create receptiveness to human obesity indicate that this disease in humans is multifaceted and deeply entrenched in biologic systems. Thus, it is almost certain that obesity has multiple causes and that there are different types of obesity. Not only does MCHR1 antagonist have potent and durable anti-obesity effects in rodents, it has surprising antidepressant and anxiolytic properties as well (Borowsky et al., Nature Medicine, 8, 825-830, 2002). MCHR1 antagonists have been reported to show antidepressant and anxiolytic activities in rodent models such as social interaction, forced swimming test and ultrasonic vocalization. These findings indicate that MCHR1 antagonists could be useful for treatment of obesity patients with multiple causes. Moreover, MCHR1 antagonists could be used to treat subjects not only with obesity, but also those with depression and anxiety. These advantages make it different from NPY receptor antagonists, with which anxiogenic-like activity can be expected, as NPY itself has anxiolytic-like effect.

Obesity is also regarded as a chronic disease and the possibly of long-term treatment is a concept that is receiving more attention. In this context, it is noteworthy that the depletion of MCH leads to hypophagia as well as leanness (Shimada et al., Nature, 396, 670-674, 1998). By contrast, NPY (Erickson et al., Nature, 381, 415-418, 1996), as well as the Y1 (Pedrazzini et al., Nature Medicine, 4, 722-726, 1998) and Y5 receptors (Marsh et al., Nature Medicine, 4, 718-721, 1998), disrupted mice maintained a stable body weight or rather became obese. Considering the above reports, MCHR1 antagonists can be more attractive than Y1 or Y5 receptor antagonists in terms of long-term treatment of obese patients.

Obesity, which is the result of an imbalance between caloric intake and energy expenditure, is highly correlated with insulin resistance and diabetes in experimental animals and human. However, the molecular mechanisms that are involved in obesity-diabetes syndromes are not clear. During early development of obesity, increase insulin secretion balances insulin resistance and protects patients from hyperglycemia (Le Stunff, et al.

Diabetes 43, 696-702 (1989)). However, after several decades, β cell function deteriorates and non-insulin-dependent diabetes develops in about 20% of the obese population (Pederson, P. *Diab. Metab. Rev.* 5, 505-509 (1989)) and (Brancati, F. L., et al., *Arch. Intern. Med.* 159, 957-963 (1999)). Given its high prevalence in modern societies, obesity has thus become the leading risk factor for NIDDM (Hill, J. O., et al., *Science* 280, 1371-1374 (1998)). However, the factors which predispose a fraction of patients to alteration of insulin secretion in response to fat accumulation remain unknown.

Whether someone is classified as overweight or obese is generally determined on the basis of their body mass index (BMI) which is calculated by dividing body weight (kg) by height squared (m^2). Thus, the units of BMI are kg/m^2 and it is possible to calculate the BMI range associated with minimum mortality in each decade of life. Overweight is defined as a BMI in the range 25-30 kg/m^2, and obesity as a BMI greater than 30 kg/m^2 (see TABLE below). There are problems with this definition in that it does not take into account the proportion of body mass that is muscle in relation to fat (adipose tissue). To account for this, obesity can also be defined on the basis of body fat content: greater than 25% and 30% in males and females, respectively.

CLASSIFICATION OF WEIGHT BY

BODY MASS INDEX (BMI)

BMI	CLASSIFICATION
< 18.5	Underweight
18.5-24.9	Normal
25.0-29.9	Overweight
30.0-34.9	Obesity (Class I)
35.0-39.9	Obesity (Class II)
>40	Extreme Obesity (Class III)

As the BMI increases there is an increased risk of death from a variety of causes

that is independent of other risk factors. The most common diseases with obesity are cardiovascular disease (particularly hypertension), diabetes (obesity aggravates the development of diabetes), gall bladder disease (particularly cancer) and diseases of reproduction. Research has shown that even a modest reduction in body weight can correspond to a significant reduction in the risk of developing coronary heart disease.

Compounds marketed as anti-obesity agents include Orlistat (XENICAL™) and Sibutramine. Orlistat (a lipase inhibitor) inhibits fat absorption directly and tends to produce a high incidence of unpleasant (though relatively harmless) side-effects such as diarrhea. Sibutramine (a mixed 5-HT/noradrenaline reuptake inhibitor) can increase blood pressure and heart rate in some patients. The serotonin releaser/reuptake inhibitors fenfluramine (Pondimin™) and dexfenfluramine (Redux™) have been reported to decrease food intake and body weight over a prolonged period (greater than 6 months). However, both products were withdrawn after reports of preliminary evidence of heart valve abnormalities associated with their use. Accordingly, there is a need for the development of a safer anti-obesity agent.

Obesity considerably increases the risk of developing cardiovascular diseases as well. Coronary insufficiency, atheromatous disease, and cardiac insufficiency are at the forefront of the cardiovascular complication induced by obesity. It is estimated that if the entire population had an ideal weight, the risk of coronary insufficiency would decrease by 25% and the risk of cardiac insufficiency and of cerebral vascular accidents by 35%. The incidence of coronary diseases is doubled in subjects less than 50 years of age who are 30% overweight. The diabetes patient faces a 30% reduced lifespan. After age 45, people with diabetes are about three times more likely than people without diabetes to have significant heart disease and up to five times more likely to have a stroke. These findings emphasize the inter-relations between risks factors for NIDDM and coronary heart disease and the potential value of an integrated approach to the prevention of these conditions based on the prevention of these conditions based on the prevention of obesity (Perry, I. J., et al., *BMJ* 310, 560-564 (1995)).

An increasing number of children and adolescents are overweight. Although not all overweight children will necessarily become overweight adults, the growing occurrence of obesity in childhood is likely to be reflected in increasing obesity in adult years. The high prevalence of obesity in our adult population and the likelihood that the nation of the future will be even more obese demands a re-examination of the health implications of this disease. See, Health Implications of Obesity. NIH Consens. Statement Online 1985 Feb 11-13; 5(9):1-7.

"Clinical obesity" is a measurement of the excess body fat relative to lean body mass and is defined as a body weight more than 20% above the ideal body weight. Recent estimates suggest that 1 in 2 adults in the United States is clinically obese, an increase of more than 25% over the past decades. Flegal M.D. et al., 22 Int. *J. Obes. Relat. Metab. Disor.* 39 (1998). Both overweight conditions and clinical obesity are a major health concerns worldwide, in particular because clinical obesity is often accompanied by numerous complications, *i.e.,* hypertension and Type II diabetes, which in turn can cause coronary artery disease, stroke, late-stage complications of diabetes and premature death. (*See*, e.g., Nishina P.M. et al., 43 *Metab.* 554 (1994)).

Although the etiologic mechanisms underlying obesity require further clarification, the net effect of such mechanisms leads to an imbalance between energy intake and expenditure. Both genetic and environmental factors are likely to be involved in the pathogenesis of obesity. These include excess caloric intake, decreased physical activity, and metabolic and endocrine abnormalities.

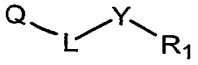
Treatment of overweight conditions and clinical obesity via pharmaceutical agents are not only of importance with respect to the conditions themselves, but also with respect to the possibility of preventing other diseases that are associated with, *e.g.*, clinical obesity, as well as enhancement of the positive feeling of "self" that often accompanies those who are overweight or clinically obese and who encounter a significant reduction in body weight. Given the foregoing discussion, it is apparent that compounds which help in the treatment of such disorders would be useful and would provide an advance in both

research and clinical medicine. The present invention is directed to these, as well as other, important ends.

Summary of the Invention

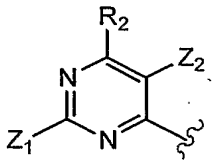
The present invention is drawn to compounds, which bind to and modulate the activity of a GPCR referred to herein as MCH, and uses thereof. The term MCH, as used herein, includes the human sequences found in GeneBank accession number NM_005297, naturally-occurring allelic variants, mammalian orthologs, biologically active fragments and recombinant mutants thereof.

One aspect of the present invention relates to certain substituted pyrimidine compounds represented by Formula (I):



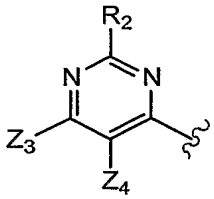
(I)

wherein Q is:



(IIa)

or



(IIb)

R_1 is selected from the group consisting of:

(i) C_{1-16} alkyl, and

C_{1-16} alkyl substituted by substituent(s) independently selected from the group consisting of:

- halogen,
- hydroxy,
- oxo,
- C_{1-5} alkoxy,

•C_{1-5} alkoxy substituted by substituent(s) independently selected from the group consisting of:

••carbocyclic aryl,

••heterocyclyl, and

••heterocyclyl substituted by C_{1-5} alkyl,

•C_{1-5} alkylcarbonyloxy,

•carbocyclyloxy,

•carbocyclic aryloxy,

•carbocyclic aryloxy substituted by substituent(s) independently selected from the group consisting of:

••halogen,

••hydroxy,

••carboxy,

••carbamoyl,

••nitro,

••cyano,

••amino,

••carbocyclic aryl,

••carbocyclic aryl substituted by C_{1-5} alkoxy,

••C_{1-5} alkoxy,

••C_{1-5} alkoxy substituted by halogen,

••C_{1-5} alkyl, and

••C_{1-5} alkyl substituted by substituent(s) independently selected from the group consisting of:

•••halogen,

•••hydroxy,

•••carboxy,

•••oxo,

•••mono-C_{1-5} alkylamino,

•••di-C_{1-5} alkylamino,

•••mono-C_{1-5} alkylamino substituted by carbocyclic aryl,

•••di-C_{1-5} alkylamino substituted by carbocyclic aryl,

•••mono-C_{1-5} alkylamino substituted by halogenated carbocyclic aryl,

•••di-C_{1-5} alkylamino substituted by halogenated carbocyclic aryl,

•••carbocyclic arylcarbonylamino, and

•••carbocyclic arylcarbonylamino substituted by halogen,

•heterocyclyloxy,

•heterocyclyloxy substituted by substituent(s) independently selected from the group consisting of:

••halogen,

••hydroxy,

••carboxy,

••carbamoyl,

••nitro,

••cyano,

••amino,

••carbocyclic aryl,

••carbocyclic aryl substituted by C_{1-5} alkoxy,

••C_{1-5} alkoxy,

••C_{1-5} alkoxy substituted by substituent(s) independently selected from the group consisting of:

- •••halogen,
- •••hydroxy, and
- •••carboxy,
- ••C_{1-5} alkyl, and
- ••C_{1-5} alkyl substituted by substituent(s) independently selected from the group consisting of:
  - •••halogen,
  - •••hydroxy, and
  - •••carboxy,
- •substituted heterocyclyl-ethylideneaminooxy,
- •C_{1-5} alkoxycarbonyl,
- •C_{1-5} alkoxycarbonyl substituted by carbocyclic aryl,
- •mono-C_{1-5} alkylaminocarbonyl,
- •di-C_{1-5} alkylaminocarbonyl,
- •mono-C_{1-5} alkylamino,
- •mono-C_{1-5} alkylamino substituted by substituent(s) independently selected from the group consisting of:
  - ••cyano,
  - ••carbocyclic aryl, and
  - ••heterocyclyl,
- •di-C_{1-5} alkylamino,
- •di-C_{1-5} alkylamino substituted by substituent(s) independently selected from the group consisting of:
  - ••cyano,
  - ••carbocyclic aryl, and
  - ••heterocyclyl,
- •mono-carbocyclic arylamino,
- •mono-carbocyclic arylamino substituted by substituent(s)

independently selected from the group consisting of:

••halogen,

••hydroxy,

••carboxy,

••carbamoyl,

••nitro,

••cyano,

••amino,

••carbocyclic aryl,

••carbocyclic aryl substituted by C_{1-5} alkoxy,

••C_{1-5} alkoxy,

••C_{1-5} alkoxy substituted by substituent(s) independently selected from the group consisting of:

•••halogen,

•••hydroxy, and

•••carboxy,

••C_{1-5} alkyl, and

••C_{1-5} alkyl substituted by substituent(s) independently selected from the group consisting of:

•••halogen,

•••hydroxy, and

•••carboxy,

•di-carbocyclic arylamino,

•di-carbocyclic arylamino substituted by substituent(s) independently selected from the group consisting of:

••halogen,

••hydroxy,

••carboxy,

••carbamoyl,

••nitro,

••cyano,

••amino,

••carbocyclic aryl,

••carbocyclic aryl substituted by C_{1-5} alkoxy,

••C_{1-5} alkoxy,

••C_{1-5} alkoxy substituted by substituent(s) independently selected from the group consisting of:

•••halogen,

•••hydroxy, and

•••carboxy,

••C_{1-5} alkyl, and

••C_{1-5} alkyl substituted by substituent(s) independently selected from the group consisting of:

•••halogen,

•••hydroxy, and

•••carboxy,

•mono-heterocyclylamino,

•mono-heterocyclylamino substituted by substituent(s) independently selected from the group consisting of:

••halogen,

••hydroxy,

••carboxy,

••carbamoyl,

••nitro,

••cyano,

••amino,

••carbocyclic aryl,

••carbocyclic aryl substituted by C_{1-5} alkoxy,

••C_{1-5} alkoxy,

••C_{1-5} alkoxy substituted by substituent(s) independently selected from the group consisting of:

•••halogen,

•••hydroxy, and

•••carboxy,

••C_{1-5} alkyl, and

••C_{1-5} alkyl substituted by substituent(s) independently selected from the group consisting of:

•••halogen,

•••hydroxy, and

•••carboxy,

-di-heterocyclylamino,

-di-heterocyclylamino substituted by substituent(s) independently selected from the group consisting of:

••halogen,

••hydroxy,

••carboxy,

••carbamoyl,

••nitro,

••cyano,

••amino,

••carbocyclic aryl,

••carbocyclic aryl substituted by C_{1-5} alkoxy,

••C_{1-5} alkoxy,

••C_{1-5} alkoxy substituted by substituent(s) independently

selected from the group consisting of:

•••halogen,

•••hydroxy, and

•••carboxy,

••C_{1-5} alkyl, and

••C_{1-5} alkyl substituted by substituent(s) independently selected from the group consisting of:

•••halogen,

•••hydroxy, and

•••carboxy,

•C_{1-5} alkylcarbonylamino,

•C_{1-5} alkylcarbonylamino substituted by substituent(s) independently selected from the group consisting of:

••C_{1-5} alkylcarbonylamino,

••carbocyclic arylcarbonylamino, and

••heterocyclyl,

•C_{1-5} alkoxycarbonylamino,

•carbocyclic arylcarbonylamino,

•heterocyclyl carbonylamino,

•carbocyclic arylsulfonylamino,

•carbocyclic arylsulfonylamino substituted by substituent(s) independently selected from the group consisting of:

••nitro,

••C_{1-5} alkyl,

••mono-C_{1-5} alkylamino, and

••di-C_{1-5} alkylamino,

•C_{1-5} alkylthio,

•C_{1-5} alkylthio substituted by substituent(s) independently selected

from the group consisting of:

••mono-carbocyclic arylaminocarbonyl,

••mono-carbocyclic arylaminocarbonyl substituted by halogen,

••di-carbocyclic arylaminocarbonyl,

••di-carbocyclic arylaminocarbonyl substituted by halogen,

••mono-carbocyclic arylamino,

••mono-carbocyclic arylamino substituted by halogen,

••di-carbocyclic arylamino,

••di-carbocyclic arylamino substituted by halogen,

••carbocyclic aryl, and

••carbocyclic aryl substituted by substituent(s) independently selected from the group consisting of:

•••halogen, and

•••C_{1-5} alkoxy,

•carbocyclic arylthio,

•carbocyclic arylthio substituted by substituent(s) independently selected from the group consisting of:

••halogen,

••C_{1-5} alkyl, and

••C_{1-5} alkyl substituted by halogen,

•carbocyclic arylsulfinyl,

•carbocyclic arylsulfinyl substituted by substituent(s) independently selected from the group consisting of:

••halogen,

••C_{1-5} alkyl, and

••C_{1-5} alkyl substituted by halogen,

•carbocyclic arylsulfonyl,

•carbocyclic arylsulfonyl substituted by substituent(s) independently selected from the group consisting of:

••halogen,

••C_{1-5} alkyl, and

••C_{1-5} alkyl substituted by halogen,

•heterocyclylthio,

•heterocyclylthio substituted by substituent(s) independently selected from the group consisting of:

••nitro, and

••C_{1-5} alkyl,

•C_{3-6} cycloalkyl,

•C_{3-6} cycloalkyl substituted by C_{1-5} alkyl,

•C_{3-6} cycloalkyl substituted by carbocyclic aryl,

•C_{3-6} cycloalkenyl,

•carbocyclyl,

•carbocyclyl substituted by substituent(s) independently selected from the group consisting of:

••halogen,

••C_{1-5} alkyl,

••C_{1-5} alkoxy,

••C_{2-5} alkenyl, and

••C_{2-5} alkenyl substituted by substituent(s) independently selected from the group consisting of:

•••carbocyclic aryl, and

•••carbocyclic aryl substituted by C_{1-5} alkylsulfinyl,

•carbocyclic aryl,

•carbocyclic aryl substituted by substituent(s) independently

selected from the group consisting of:

••halogen,

••hydroxy,

••carboxy,

••carbamoyl,

••cyano,

••nitro,

••amino,

••C_{1-5} alkylcarbonylamino,

••C_{3-6} cycloalkylcarbonylamino,

••C_{1-5} alkyl,

••C_{1-5} alkyl substituted by substituent(s) independently selected from the group consisting of:

•••halogen,

•••hydroxy,

•••carboxy,

•••carbamoyl,

•••oxo,

•••carbocyclic aryl,

•••heterocyclyl,

•••mono-carbocyclic arylamino,

•••di-carbocyclic arylamino,

•••mono-carbocyclic arylamino substituted by substituent(s) independently selected from the group consisting of:

••••halogen,

••••nitro,

••••C_{1-5} alkyl,

••••C_{1-5} alkoxy, and

••••C_{1-5} alkoxy substituted by halogen,

•••di-carbocyclic arylamino substituted by substituent(s) independently selected from the group consisting of:

••••halogen,

••••nitro,

••••C_{1-5} alkyl,

••••C_{1-5} alkoxy, and

••••C_{1-5} alkoxy substituted by halogen,

••C_{2-5} alkenyl,

••C_{1-5} alkoxy,

••C_{1-5} alkoxy substituted by substituent(s) independently selected from the group consisting of:

•••halogen, and

•••carbocyclic aryl,

••carbocyclic aryloxy,

••C_{1-5} alkoxycarbonyl,

••C_{1-5} alkylcarbonyloxy,

••mono-C_{1-5} alkylamino,

••di-C_{1-5} alkylamino,

••mono-carbocyclic arylamino,

••mono-carbocyclic arylamino substituted by halogen,

••di-carbocyclic arylamino,

••di-carbocyclic arylamino substituted by halogen,

••mono-carbocyclic arylaminocarbonyl,

••mono-carbocyclic arylaminocarbonyl substituted by substituent(s) selected from the group consisting of:

•••halogen,

•••nitro,

•••C_{1-5} alkyl,

•••C_{1-5} alkoxy, and

•••C_{1-5} alkoxy substituted by halogen,

••di-carbocyclic arylaminocarbonyl,

••di-carbocyclic arylaminocarbonyl substituted by substituent(s) selected from the group consisting of:

•••halogen,

•••nitro,

•••C_{1-5} alkyl,

•••C_{1-5} alkoxy, and

•••C_{1-5} alkoxy substituted by halogen,

••mercapto,

••C_{1-5} alkylthio,

••C_{1-5} alkylthio substituted by halogen,

••C_{1-5} alkylsulfonyl,

••C_{3-6} cycloalkyl,

••carbocyclic aryl, and

••heterocyclyl,

•heterocyclyl, and

•heterocyclyl substituted by substituent(s) independently selected from the group consisting of:

••halogen,

••hydroxy,

••carboxy,

••carbamoyl,

••cyano,

••nitro,

••amino,

••C_{1-5} alkyl,

••C_{1-5} alkyl substituted by substituent(s) independently selected from the group consisting of:

•••halogen,

•••hydroxy,

•••carboxy, and

•••carbamoyl,

••C_{1-5} alkyl substituted by carbocyclic aryl,

••C_{1-5} alkoxy,

••C_{1-5} alkoxy substituted by halogen,

••C_{1-5} alkoxy substituted by carbocyclic aryl,

••carbocyclic aryl, and

••carbocyclic aryl substituted by halogen,

(ii) C_{2-8} alkenyl, and

C_{2-8} alkenyl substituted by substituent(s) independently selected from the group consisting of:

•halogen,

•oxo,

•C_{1-5} alkoxy,

•C_{1-5} alkoxy substituted by carbocyclic aryl,

•carbocyclic aryl,

•carbocyclic aryl substituted by substituent(s) independently selected from the group consisting of:

••halogen,

••hydroxy,

••nitro,

••C_{1-5} alkyl,

••C_{1-5} alkyl substituted by halogen,

••C_{1-5} alkoxy, and

••C_{1-5} alkoxy substituted by halogen,

•heterocyclyl, and

•heterocyclyl substituted by substituent(s) independently selected from the group consisting of:

••hydroxy,

••nitro,

••C_{1-5} alkyl, and

••C_{1-5} alkoxy,

(iii) C_{2-5} alkynyl, and

C_{2-5} alkynyl substituted by carbocyclic aryl,

(iv) C_{3-12} cycloalkyl, and

C_{3-12} cycloalkyl substituted by substituent(s) independently selected from the group consisting of:

•C_{1-5} alkyl,

•C_{1-5} alkyl substituted by substituent(s) independently selected from the group consisting of:

••hydroxy,

••oxo, and

••carbocyclic aryl,

•mono-C_{1-5} alkylamino,

•mono-C_{1-5} alkylamino substituted by carbocyclic aryl,

•di-C_{1-5} alkylamino,

•di-C_{1-5} alkylamino substituted by carbocyclic aryl,

•carbocyclic arylcarbonylamino,

•carbocyclic aryl, and

•carbocyclic aryl substituted by halogen,

(v) C_{3-6} cycloalkenyl, and

C_{3-6} cycloalkenyl substituted by C_{1-5} alkyl,

(vi) carbocyclyl, and

carbocyclyl substituted by substitutent(s) independently selected from the group consisting of:

•hydroxy, and

•nitro,

(vii) carbocyclic aryl, and

carbocyclic aryl substituted by substituent(s) independently selected from the group consisting of:

•halogen,

•hydroxy,

•cyano,

•nitro,

•C_{1-10} alkyl,

•C_{1-10} alkyl substituted by substituent(s) independently selected from the group consisting of:

••halogen,

••hydroxy,

••carboxy,

••carbamoyl,

••oxo,

••C_{1-5} alkoxy,

••carbocyclic aryloxy,

••mono-C_{1-5} alkylamino-N-oxy,

••di-C_{1-5} alkylamino-N-oxy,

••mono-C_{1-5} alkylamino,

••di-C_{1-5} alkylamino,

••mono-C_{1-5} alkylamino substituted by carbocyclic aryl,

••di-C_{1-5} alkylamino substituted by carbocyclic aryl,

••mono-carbocyclic arylamino,

••di-carbocyclic arylamino,

••carbocyclylimino,

••carbocyclylimino substituted by carbocyclic aryl,

••mono-carbocyclic arylamino,

••di-carbocyclic arylamino,

••mono-carbocyclic arylamino substituted by C_{1-5} alkoxy,

••di-carbocyclic arylamino substituted by C_{1-5} alkoxy,

••mono-carbocyclic arylaminocarbonyl,

••di-carbocyclic arylaminocarbonyl,

••mono-carbocyclic arylaminocarbonyl substituted by C_{1-5} alkoxy,

••di-carbocyclic arylaminocarbonyl substituted by C_{1-5} alkoxy,

••carbocyclic aryl,

••carbocyclic aryl substituted by substituent(s) independently selected from the group consisting of:

•••halogen,

•••C_{1-5} alkyl, and

•••C_{1-5} alkyl substituted by halogen,

••heterocyclyl, and

••heterocyclyl substituted by C_{1-5} alkyl,

•C_{2-5} alkenyl,

•C_{2-5} alkenyl substituted by carbocyclic aryl,

•C_{1-9} alkoxy,

•C_{1-9} alkoxy substituted by substituent(s) independently selected from the group consisting of:

••hydroxy,

••halogen,

••carboxy,

••mono-C_{1-5} alkylamino,

••di-C_{1-5} alkylamino,

••carbocyclic aryl,

••halogenated carbocyclic aryl,

••heterocyclyl,

••heterocyclyl substituted by substituent(s) independently selected from the group consisting of:

•••halogen,

•••heterocyclyl, and

•••heterocyclyl substituted by substituent(s) independently selected from the group consisting of:

••••halogen,

••••C_{1-5} alkyl, and

••••C_{1-5} alkyl substituted by halogen,

•C_{2-5} alkenyloxy,

•C_{3-6} cycloalkoxy,

•C_{1-5} alkylcarbonyloxy,

•carbocyclic aryloxy,

•carbocyclic aryloxy substituted by substituent(s) independently selected from the group consisting of:

••halogen,

••hydroxy,

••carboxy,

••carbamoyl,

••cyano,

••nitro,

••amino,

••C_{1-5} alkyl,

••C_{1-5} alkyl substituted by substituent(s) independently selected from the group consisting of:

•••halogen,

•••hydroxy,

•••carboxy, and

•••carbamoyl,

••C_{1-5} alkoxy, and

••C_{1-5} alkoxy substituted by halogen,

•heterocyclyloxy,

•heterocyclyloxy substituted by substituent(s) independently selected from the group consisting of:

••halogen,

••hydroxy,

••carboxy,

••carbamoyl,

••cyano,

••nitro,

••amino,

••C_{1-5} alkyl,

••C_{1-5} alkyl substituted by substituent(s) independently selected from the group consisting of:

•••halogen,

•••hydroxy,

•••carboxy, and

•••carbamoyl,

••C_{1-5} alkoxy, and

••C_{1-5} alkoxy substituted by halogen,

•(carbocyclic aryl)$S(O)_2O$,

•carboxy,

•carbamoyl,

•C_{1-5} alkoxycarbonyl,

•mono-C_{1-5} alkylaminocarbonyl,

•di-C_{1-5} alkylaminocarbonyl,

•mono-C_{1-5} alkylaminocarbonyl substituted by carbocyclic aryl,

•di-C_{1-5} alkylaminocarbonyl substituted by carbocyclic aryl,

•mono-carbocyclic arylaminocarbonyl,

•di-carbocyclic arylaminocarbonyl,

•mono-carbocyclic arylaminocarbonyl substituted by C_{1-5} alkyl,

•di-carbocyclic arylaminocarbonyl substituted by C_{1-5} alkyl,

•amino,

•mono-C_{1-5} alkylamino,

•di-C_{1-5} alkylamino,

•mono-C_{1-5} alkylamino substituted by cyano,

•di-C_{1-5} alkylamino substituted by cyano,

•mono-carbocyclic arylamino,

•di-carbocyclic arylamino,

•C_{1-5} alkylcarbonylamino,

•C_{3-6} cycloalkylcarbonylamino,

•C_{2-5} alkynylcarbonylamino,

•C_{2-5} alkynylcarbonylamino substituted by carbocyclic aryl,

- C_{1-5} alkoxycarbonylamino,
- carbocyclic arylsulfonylamino,
- carbocyclic arylsulfonylamino substituted by C_{1-5} alkyl,
- (carbocyclic aryl)NHC(O)NH,
- (carbocyclic aryl)NHC(O)NH substituted by C_{1-5} alkoxy,
- (carbocyclic aryl)NHC(O)NH substituted by haloganated C_{1-5} alkoxy,
- carbocyclic aryl azo,
- carbocyclic aryl azo substituted by mono-C_{1-5} alkylamino,
- carbocyclic aryl azo substituted by di-C_{1-5} alkylamino,
- C_{1-5} alkylthio,
- C_{1-5} alkylthio substituted by halogen,
- carbocyclic arylthio,
- carbocyclic arylthio substituted by substituent(s) independently selected from the group consisting of:
  - halogen,
  - nitro,
  - cyano, and
  - C_{1-5} alkyl,
- aminosulfonyl,
- heterocyclylthio,
- C_{1-5} alkylsulfonyl,
- mono-C_{1-5} alkylaminosulfonyl,
- di-C_{1-5} alkylaminosulfonyl,
- heterocyclylsulfonyl,
- C_{3-6} cycloalkyl,
- C_{3-6} cycloalkyl substituted by C_{1-5} alkyl,
- carbocyclic aryl,

•carbocyclic aryl substituted by substituent(s) independently selected from the group consisting of:

••C_{1-7} alkyl, and

••C_{1-7} alkyl substituted by halogen,

•heterocyclyl, and

•heterocyclyl substituted by substituent(s) independently selected from the group consisting of:

••C_{1-5} alkyl,

••carbocyclic aryl, and

••halogenated carbocyclic aryl,

•C_{1-5} alkoxycarbonyl substituted by carbocyclic aryl, and

(viii) heterocyclyl, and

heterocyclyl substituted by substituent(s) independently selected from the group consisting of:

•halogen,

•hydroxy,

•carboxy,

•carbamoyl,

•cyano,

•nitro,

•amino,

•C_{1-5} alkyl,

•C_{1-5} alkyl substituted by substituent(s) independently selected from the group consisting of:

••halogen,

••hydroxy,

••carboxy,

••carbamoyl,

••oxo,

••C_{1-5} alkylcarbonyloxy,

••carbocyclic arylcarbonylamino,

••carbocyclic arylcarbonylamino substituted by halogen,

••C_{1-5} alkoxycarbonyl,

••C_{1-5} alkylthio,

••C_{1-5} alkylthio substituted by carbocyclic aryl,

••C_{1-5} alkylthio substituted by halogenated carbocyclic aryl,

••carbocyclic aryl,

••carbocyclic aryl substituted by substituent(s) independently selected from the group consisting of:

•••halogen, and

•••nitro,

••heterocyclyl, and

••heterocyclyl substituted by substituent(s) independently selected from the group consisting of:

•••halogen,

•••C_{1-5} alkyl, and

•••C_{1-5} alkyl substituted by halogen,

•C_{1-5} alkoxy,

•C_{1-5} alkoxy substituted by halogen,

•C_{1-5} alkoxy substituted by carbocyclic aryl,

•carbocyclic aryloxy,

•carbocyclic aryloxy substituted by substituent(s) independently selected from the group consisting of:

••halogen,

••nitro,

••cyano,

••hydroxy,

••carboxy,

••carbamoyl,

••amino,

••C_{1-5} alkyl,

••C_{1-5} alkyl substituted by substituent(s) independently selected from the group consisting of:

•••halogen,

•••hydroxy,

•••carboxy, and

•••carbamoyl,

••mono-C_{1-5} alkylamino,

••di-C_{1-5} alkylamino,

••C_{1-5} alkylcarbonylamino,

••C_{3-6} cycloalkycarbonylamino,

••C_{1-5} alkoxy,

••C_{1-5} alkoxy substituted by halogen,

••C_{3-6} cycloalkyl,

••C_{2-5} alkenyl,

••C_{2-5} alkynyl,

••carboxy,

••C_{1-5} alkoxycarbonyl,

••mono-C_{1-5} alkylaminocarbonyl,

••di-C_{1-5} alkylaminocarbonyl,

••mono-C_{3-6} cycloalkylaminocarbonyl,

••di-C_{3-6} cycloalkylaminocarbonyl,

••mono-C_{1-5} alkylaminocarbonylamino,

••di-C_{1-5} alkylaminocarbonylamino,

••mono-C_{3-6} cycloalkylaminocarbonylamino,

••di-C_{3-6} cycloalkylaminocarbonylamino,

••C_{1-5} alkylthio,

••C_{1-5} alkylthio substituted by halogen,

••C_{1-5} alkylsulfinyl,

••C_{1-5} alkylsulfinyl substituted by halogen,

••C_{1-5} alkylsulfonyl, and

••C_{1-5} alkylsulfonyl substituted by halogen,

•heterocyclyloxy,

•heterocyclyloxy substituted by substituent(s) independently selected from the group consisting of:

••halogen,

••nitro,

••hydroxy,

••carboxy,

••carbamoyl,

••cyano,

••amino,

••C_{1-5} alkyl,

••C_{1-5} alkyl substituted by substituent(s) independently selected from the group consisting of:

•••halogen,

•••hydroxy,

•••carboxy, and

•••carbamoyl,

••C_{1-5} alkoxy, and

••C_{1-5} alkoxy substituted by halogen,

•mono-C_{1-5} alkylamino,

•di-C_{1-5} alkylamino,

•C_{1-5} alkylcarbonylamino,

•C_{1-5} alkylthio,

•C_{2-5} alkenylthio,

•carbocyclic arylthio,

•carbocyclic arylthio substituted by halogen,

•carbocyclic arylthio substituted by C_{1-5} alkoxycarbonyl,

•heterocyclylthio,

•heterocyclylthio substituted by C_{1-5} alkyl,

•C_{1-5} alkylsulfinyl,

•C_{1-5} alkylsulfonyl,

•carbocyclic arylsulfinyl,

•carbocyclic arylsulfinyl substituted by halogen,

•carbocyclic arylsulfonyl,

•carbocyclic arylsulfonyl substituted by halogen,

•carbocyclic arylsulfonyl substituted by C_{1-5} alkyl,

•C_{1-5} alkoxycarbonyl,

•C_{1-5} alkoxycarbonyl substituted by carbocyclic aryl,

•carbocyclic aryl,

•carbocyclic aryl substituted by substituent(s) independently selected from the group consisting of:

••halogen,

••nitro,

••C_{1-5} alkyl,

••C_{1-5} alkyl substituted by halogen,

••C_{1-5} alkoxy, and

••C_{1-5} alkoxy substituted by halogen,

•heterocyclyl, and

•heterocyclyl substituted by substituent(s) independently selected from the group consisting of:

••halogen,

••C_{1-5} alkyl,

••C_{1-5} alkyl substituted by halogen,

••C_{1-5} alkoxy, and

••C_{1-5} alkoxycarbonyl;

R_2 is halogen, C_{1-5} alkyl, C_{1-5} alkyl substituted by halogen, C_{1-5} alkyl substituted by hydroxy, C_{1-5} alkyl substituted by carbocyclic aryl, C_{1-5} alkyl substituted by halogenated carbocyclic aryl, C_{1-5} alkyl substituted by heterocyclyl, C_{1-5} alkyl substituted by halogenated heterocyclyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{1-5} alkoxy, C_{1-5} alkoxy substituted by halogen, C_{1-5} alkylthio, $-N(R_{2a})(R_{2b})$; wherein R_{2a} and R_{2b} are each independently hydrogen, C_{1-5} alkyl, or C_{1-5} alkyl substituted by substituent(s) independently selected from the group consisting of:

•halogen,

•hydroxy,

•carboxy,

•carbamoyl,

•C_{1-5} alkoxy,

•amino,

•C_{3-6} cycloalkyl,

•carbocyclic aryl,

•carbocyclic aryl substituted by substituent(s) independently selected from the group consisting of:

••halogen,

••C_{1-5} alkyl,

••C_{1-5} alkoxy,

••C_{1-5} alkyl substituted by halogen,

••C_{1-5} alkoxy substituted by halogen, and

••$-SO_2NH_2$,

•heterocyclyl, and

•heterocyclyl substituted by substituent(s) independently selected from the group consisting of:

••halogen,

••C_{1-5} alkyl,

••C_{1-5} alkoxy,

••C_{1-5} alkyl substituted by halogen, and

••C_{1-5} alkoxy substituted by halogen,

C_{3-6} cycloalkyl, carbocyclic aryl, carbocyclic aryl substituted by substituent(s) independently selected from the group consisting of:

•halogen,

•C_{1-5} alkyl,

•C_{1-5} alkoxy,

•C_{1-5} alkyl substituted by halogen, and

•C_{1-5} alkoxy substituted by halogen,

heterocyclyl, or heterocyclyl substituted by substituent(s) independently selected from the group consisting of:

•halogen,

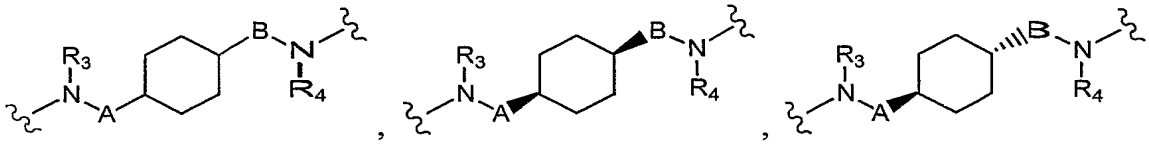
•C_{1-5} alkyl,

•C_{1-5} alkoxy,

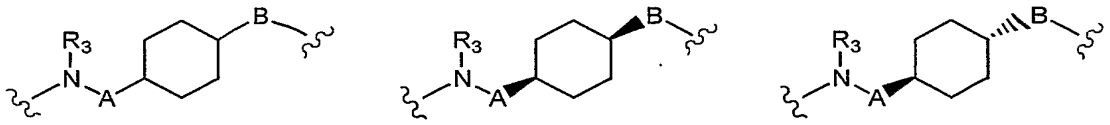
•C_{1-5} alkyl substituted by halogen, and

•C_{1-5} alkoxy substituted by halogen;

L is selected from the group consisting of Formulae (III), (IIIa), (IIIb), (IV), (IVa), and (IVb);



(III) (IIIa) (IIIb)



(IV) (IVa) (IVb)

wherein R_3 and R_4 are each independently hydrogen or C_{1-5} alkyl; and A and B are each independently a single bond, $-CH_2-$, or $-(CH_2)_2-$;

Z_1, Z_2, Z_3, and Z_4 are each independently hydrogen, halogen, C_{1-5} alkyl, C_{1-5} alkyl substituted by halogen, C_{1-5} alkyl substituted by hydroxy, C_{1-5} alkyl substituted by carbocyclic aryl, C_{1-5} alkyl substituted by halogenated carbocyclic aryl, C_{1-5} alkyl substituted by heterocyclyl, C_{1-5} alkyl substituted by halogenated heterocyclyl, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{3-6} cycloalkyl, C_{1-5} alkoxy, C_{1-5} alkoxy substituted by halogen, mono-C_{1-5} alkyl amino, di-C_{1-5} alkyl amino, C_{1-5} alkylthio, carbocyclic aryl, substituted carbocyclic aryl, heterocyclyl, or substituted heterocyclyl; or R_2 and Z_2 are bonded to each other to form a ring and $-R_2-Z_2-$ is $-(CH_2)n-$ or $-(CH_2)o-CH=CH-(CH_2)p-$; wherein one $-CH_2-$ group of $-R_2-Z_2-$ can optionally be replaced by C(O), NR_6, O, S, S(O), or $S(O)_2$; wherein n is 2, 3, 4, 5, or 6; o and p are each independently 0, 1, 2, 3, or 4 provided that

o+p = 0, 1, 2, 3, or 4; and R_6 is hydrogen, C_{1-5} alkyl, or substituted C_{1-5} alkyl;

and

Y represents:

(i) $-C(O)NR_5-$, $-C(S)NR_5-$, $-C(O)O-$, $-S(O)_2-$, $-C(O)-$, $-C(S)-$, or $-(CH_2)_m-$ when L is selected from the group consisting of Formulae (III), (IIIa), and (IIIb); or

(ii) $-C(O)NR_5-$, $-C(S)NR_5-$, $-C(O)O-$, or $-OC(O)-$ when L is selected from the group consisting of Formulae (IV), (IVa), and (IVb);

wherein R_5 is hydrogen or C_{1-5} alkyl; and m is 0, 1, 2, 3, 4, or 5;

wherein carbocyclic aryl is phenyl, naphthyl, anthranyl, phenanthryl, or biphenyl;

carbocyclyl is 10,11-dihydro-5-oxo-dibenzo[a,d]cycloheptyl, 1-oxo-indanyl, 7,7-dimethyl-2-oxo-bicyclo[2.2.1]heptyl, 9*H*-fluorenyl, 9-oxo-fluorenyl, acenaphthyl, anthraquinonyl, *C*-fluoren-9-ylidene, indanyl, indenyl, menthyl, 1,2,3,4-tetrahydro-naphthyl, or bicyclo[2.2.1]heptenyl;

heterocyclyl is 1,2,3,4-tetrahydro-isoquinolyl, 1,2,3-thiadiazolyl, 1,2,3-triazolyl, 1,2-dihydro-3-oxo-pyrazolyl, 1,3,4-thiadiazolyl, 1,3-dioxo-isoindolyl, 1,3-dioxolanyl, 1*H*-indolyl, 1*H*-pyrrolo[2,3-c]pyridyl, 1*H*-pyrrolyl, 1-oxo-3*H*-isobenzofuranyl, 2,2',5',2"-terthiophenyl, 2,2'-bithiophenyl, 2,3-dihydro-1-oxo-isoindolyl, 2,3-dihydro-benzo[1,4]dioxinyl, 2,3 –dihydro-benzofuryl, 2,4-dihydro-3-oxo-pyrazolyl, 2*H*-benzopyranyl, 2-oxo-benzopyranyl, 2-oxo-pyrrolidinyl, 3,4-dihydro-2*H*-benzo[1,4]oxazinyl, 3,4-dihydro-2*H*-benzo[b][1,4]dioxepinyl, 4*H*-benzo[1,3]dioxinyl, 4*H*–benzopyranyl, 4-oxo-1,5,6,7-tetrahydro-indolyl, 4-oxo-3,4-dihydro-phthalazinyl, 4-oxo-benzopyranyl, 9,10,10-trioxo-thioxanthenyl, 9*H*-carbazolyl, 9*H*-xanthenyl, azetidinyl, benzimidazolyl,

benzo[1,3]dioxolyl, benzo[2,1,3]oxadiazolyl, benzo[1,2,5]oxadiazolyl, benzo[b]thienyl, benzofuryl, benzothiazolyl, cinnolyl, furyl, imidazo[2,1-b]thiazolyl, imidazolyl, isoxazolyl, morpholino, morpholinyl, oxazolyl, oxolanyl, piperazyl, piperidyl, piridyl, pyrazolo[5,1-b]thiazolyl, pyrazolyl, pyrazinyl, pyridyl, pyrimidyl, pyrrolidyl, quinolyl, quinoxalyl, thiazolidyl, thiazolyl, thienyl, thiolanyl, 2,3-dihydro-benzofuryl, tetrahydro-thienyl, or benzofuranyl;

halogen is fluoro, chloro, bromo, or iodo;

or a pharmaceutically acceptable salt, hydrate, or solvate thereof.

One aspect of the present invention pertains to pharmaceutical compositions comprising a therapeutically effective amount of at least one compound, as described herein, in combination with a pharmaceutically acceptable carrier.

One aspect of the present invention pertains to methods for the prophylaxis or treatment of improving memory function, sleeping and arousal, anxiety, depression, mood disorders, seizure, obesity, diabetes, appetite and eating disorders, cardiovascular disease, hypertension, dyslipidemia, myocardial infarction, binge eating disorders including bulimia, anorexia, mental disorders including manic depression, schizophrenia, delirium, dementia, stress, cognitive disorders, attention deficit disorder, substance abuse disorders and dyskinesias including Parkinson's disease, epilepsy, and addiction comprising administering to an individual suffering from said condition a therapeutically effective amount of a compound, as described herein, or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for the prophylaxis or treatment of an eating disorder, obesity or an obesity related disorder comprising administering to an individual suffering from the condition a therapeutically effective amount of a compound, as described herein, or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for the prophylaxis or treatment of anxiety, depression, schizophrenia, addiction, or epilepsy comprising administering to an individual suffering from the condition a therapeutically effective

amount of a compound, as described herein, or a pharmaceutical composition.

One aspect of the present invention pertains to compounds of the present invention, as described herein, or a pharmaceutical composition thereof, for use in a method of treatment of the human or animal body by therapy.

One aspect of the present invention pertains to compounds of the present invention, as described herein, or a pharmaceutical composition thereof, for use in a method of prophylaxis or treatment of an eating disorder, obesity or an obesity related disorder of the human or animal body by therapy.

One aspect of the present invention pertains to compounds of the present invention, as described herein, or a pharmaceutical composition thereof, for use in a method of prophylaxis or treatment of anxiety, depression, schizophrenia, addiction, or epilepsy of the human or animal body by therapy.

One aspect of the present invention pertains to compounds of the present invention, as described herein, for the manufacture of a medicament for use in the prophylaxis or treatment of an eating disorder, obesity or obesity related disorders.

One aspect of the present invention pertains to compounds of the present invention, as described herein, for the manufacture of a medicament for use in the prophylaxis or treatment of anxiety, depression, schizophrenia, addiction, or epilepsy.

One aspect of the present invention pertains to methods of decreasing food intake of an individual comprising administering to the individual a therapeutically effective amount of a compound, as described herein, or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods of inducing satiety in an individual comprising administering to said individual a therapeutically effective amount of a compound, as described herein, or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods of controlling or reducing weight gain in an individual comprising administering to said individual a therapeutically effective amount of a compound, as described herein, or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods of modulating a MCH receptor in an individual comprising contacting the receptor with a compound, as described herein. In some embodiments, the compound is an antagonist. In some embodiments, the modulation of the MCH receptor is for the prophylaxis or treatment of an eating disorder, obesity or obesity related disorder. In some embodiments, the modulation of the MCH receptor reduces food intake of the individual. In some embodiments, the modulation of the MCH receptor induces satiety in the individual. In some embodiments, the modulation of the MCH receptor controls or reduces weight gain of the individual. In some embodiments, the modulation of the MCH receptor is for prophylaxis or treatment of anxiety, depression, schizophrenia, addiction, or epilepsy.

In some embodiments, the individual is a mammal.

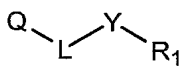
In some embodiments, the mammal is a human.

In some embodiments, the human has a body mass index of about 18.5 to about 45. In some embodiments, the human has a body mass index of about 25 to about 45. In some embodiments, the human has a body mass index of about 30 to about 45. In some embodiments, the human has a body mass index of about 35 to about 45.

One aspect of the present invention pertains to methods of producing a pharmaceutical composition comprising admixing a compound, as described herein, and a pharmaceutically acceptable carrier.

Detailed Description of the Invention

One aspect of the present invention relates to certain substituted pyrimidine compounds represented by Formula (I):



(I)

or a pharmaceutically acceptable salt, hydrate or solvate thereof, wherein Q, L, Y, and R_1 are as described herein, *supra* and *infra*.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination.

In some embodiments, compounds of the present invention are of Formula (I) wherein Q is Formula (IIa); Z_1 is hydrogen, halogen, C_{1-5} alkyl, C_{1-5} alkyl substituted by halogen, C_{3-6} cycloalkyl, C_{1-5} alkoxy, C_{1-5} alkoxy substituted by halogen, or C_{1-5} alkylthio or a pharmaceutically acceptable salt, hydrate, or solvate thereof.

In some embodiments, compounds of the present invention are of Formula (I) wherein R_1 is selected from the group consisting of:

(i) C_{1-10} alkyl, and

C_{1-10} alkyl substituted by substituent(s) independently selected from the group consisting of:

- halogen,
- oxo,
- C_{1-5} alkoxy,
- C_{1-5} alkoxy substituted by carbocyclic aryl,
- C_{1-5} alkylcarbonyloxy,
- C_{1-5} alkoxycarbonyl,
- C_{1-5} alkoxycarbonyl substituted by carbocyclic aryl,
- carbocyclic aryloxy, and
- carbocyclic aryloxy substituted by substituent(s) independently selected from the group consisting of:
  - halogen,
  - nitro,
  - C_{1-5} alkyl, and
  - C_{1-5} alkyl substituted by oxo,

•heterocyclyloxy,

•heterocyclyloxy substituted by C_{1-5} alkyl,

•mono-carbocyclic arylamino,

•di-carbocyclic arylamino,

•carbocyclic arylsulfonylamino,

•carbocyclic arylsulfonylamino substituted by C_{1-5} alkyl,

•C_{1-5} alkylthio,

•C_{1-5} alkylthio substituted by carbocyclic aryl,

•carbocyclic arylthio,

•carbocyclic arylthio substituted by halogen,

•carbocyclic arylthio substituted by C_{1-5} alkyl,

•carbocyclic arylsulfonyl,

•carbocyclic arylsulfonyl substituted by halogen,

•heterocyclylthio,

•heterocyclylthio substituted by C_{1-5} alkyl,

•C_{3-6} cycloalkyl,

•C_{3-6} cycloalkenyl,

•carbocyclyl,

•carbocyclyl substituted by C_{1-5} alkoxy,

•carbocyclic aryl, and

•carbocyclic aryl substituted by substituent(s) independently selected from the group consisting of:

••halogen,

••nitro,

••C_{1-5} alkyl, and

••C_{1-5} alkyl substituted by substituent(s) independently selected from the group consisting of:

•••halogen,

•••carbocyclic aryl, and

•••heterocyclyl,

••C_{1-5} alkoxy,

••C_{1-5} alkoxy substituted by halogen,

••C_{1-5} alkoxy substituted by carbocyclic aryl,

••carbocyclic aryloxy,

••mono-carbocyclic arylaminocarbonyl, and

••mono-carbocyclic arylaminocarbonyl substituted by substituent(s) selected from the group consisting of:

•••halogen,

•••C_{1-5} alkyl,

•••C_{1-5} alkoxy, and

•••C_{1-5} alkoxy substituted by halogen,

••di-carbocyclic arylaminocarbonyl, and

••di-carbocyclic arylaminocarbonyl substituted by substituent(s) selected from the group consisting of:

•••halogen,

•••C_{1-5} alkyl,

•••C_{1-5} alkoxy, and

•••C_{1-5} alkoxy substituted by halogen,

••C_{1-5} alkylthio,

••C_{1-5} alkylthio substituted by halogen,

••C_{1-5} alkylsulfonyl,

••carbocyclic aryl, and

••heterocyclyl,

•heterocyclyl, and

•heterocyclyl substituted by substituent(s) independently selected from the group consisting of:

••C_{1-5} alkyl,

••C_{1-5} alkoxy,

••C_{1-5} alkoxy substituted by carbocyclic aryl,

••carbocyclic aryl, and

••carbocyclic aryl substituted by halogen,

(ii) C_{2-5} alkenyl, and

C_{2-5} alkenyl substituted by substituent(s) independently selected from the group consisting of:

•carbocyclic aryl, and

•carbocyclic aryl substituted by substituent(s) independently selected from the group consisting of:

••nitro,

••halogen,

••C_{1-5} alkyl,

••C_{1-5} alkyl substituted by halogen,

••C_{1-5} alkoxy, and

••C_{1-5} alkoxy substituted by halogen,

(iii) C_{3-6} cycloalkyl, and

C_{3-6} cycloalkyl substituted by substituent(s) independently selected from the group consisting of:

•C_{1-5} alkyl,

•C_{1-5} alkyl substituted by carbocyclic aryl,

•carbocyclic arylcarbonylamino, and

•carbocyclic aryl,

(iv) carbocyclyl, and

carbocyclyl substituted by nitro,

(v) carbocyclic aryl, and

carbocyclic aryl substituted by substituent(s) independently

selected from the group consisting of:

•halogen,

•cyano,

•nitro,

•C_{1-9} alkyl, and

•C_{1-9} alkyl substituted by substituent(s) independently selected from the group consisting of:

••halogen,

••oxo,

••mono-carbocyclic arylaminocarbonyl,

••di-carbocyclic arylaminocarbonyl,

••mono-carbocyclic arylaminocarbonyl substituted by C_{1-5} alkoxy,

••di-carbocyclic arylaminocarbonyl substituted by C_{1-5} alkoxy,

••carbocyclic aryloxy,

••carbocyclic aryl, and

••carbocyclic aryl substituted by substituent(s) independently selected from the group consisting of:

•••halogen,

•••C_{1-5} alkyl, and

•••C_{1-5} alkyl substituted by halogen,

••heterocyclyl, and

••heterocyclyl substituted by C_{1-5} alkyl,

•C_{2-5} alkenyl,

•C_{1-7} alkoxy,

•C_{1-7} alkoxy substituted by halogen,

•C_{1-7} alkoxy substituted by carbocyclic aryl,

•C_{3-6} cycloalkoxy,

•carbocyclic aryloxy, and

•carbocyclic aryloxy substituted by substituent(s) independently selected from the group consisting of:

••halogen,

••nitro, and

••C_{1-5} alkoxy

•heterocyclyloxy, and

•heterocyclyloxy substituted by substituent(s) independently selected from the group consisting of:

••halogen,

••C_{1-5} alkyl, and

••C_{1-5} alkyl substituted by halogen,

•C_{1-5} alkoxycarbonyl,

•mono-C_{1-5} alkylaminocarbonyl,

•di-C_{1-5} alkylaminocarbonyl,

•mono-C_{1-5} alkylaminocarbonyl substituted by carbocyclic aryl,

•di-C_{1-5} alkylaminocarbonyl substituted by carbocyclic aryl,

•mono-carbocyclic arylaminocarbonyl,

•di-carbocyclic arylaminocarbonyl,

•mono-carbocyclic arylaminocarbonyl substituted by C_{1-5} alkyl,

•di-carbocyclic arylaminocarbonyl substituted by C_{1-5} alkyl,

•mono-C_{1-5} alkylamino,

•di-C_{1-5} alkylamino,

•C_{1-5} alkylthio,

•C_{1-5} alkylthio substituted by halogen,

•C_{1-5} alkylsulfonyl,

•carbocyclic aryl, and

•carbocyclic aryl substituted by substituent(s) independently selected from the group consisting of:

••C_{1-7} alkyl, and

••C_{1-7} alkyl substituted by halogen,

(vi) heterocyclyl, and

heterocyclyl substituted by substituent(s) independently selected from the group consisting of:

•halogen,

•C_{1-5} alkyl, and

•C_{1-5} alkyl substituted by substituent(s) independently selected from the group consisting of:

••halogen,

••oxo,

••carbocyclic aryl,

••carbocyclic aryl substituted by halogen,

••heterocyclyl, and

••heterocyclyl substituted by substituent(s) independently selected from the group consisting of:

•••halogen,

•••C_{1-5} alkyl, and

•••C_{1-5} alkyl substituted by halogen,

•C_{1-5} alkoxy,

•C_{1-5} alkylthio,

•carbocyclic arylthio,

•C_{1-5} alkylsulfonyl,

•carbocyclic arylsulfonyl,

•carbocyclic arylsulfonyl substituted by halogen,

•carbocyclic arylsulfonyl substituted by C_{1-5} alkyl,

•C_{1-5} alkoxycarbonyl,

•carbocyclic aryl, and

•carbocyclic aryl substituted by substituent(s) independently selected from the group consisting of:

••halogen,

••nitro, and

••C_{1-5} alkyl,

•heterocyclyl, and

•heterocyclyl substituted by substituent(s) independently selected from the group consisting of:

••halogen,

••C_{1-5} alkyl, and

••C_{1-5} alkyl substituted by halogen;

wherein carbocyclic aryl is phenyl, naphthyl, or anthranyl;

carbocyclyl is 1-oxo-indanyl, 9*H*-fluorenyl, 9-oxo-fluorenyl, anthraquinonyl, *C*-fluoren-9-ylidene, indanyl, or menthyl;

heterocyclyl is 1,2,3,4-tetrahydro-isoquinolyl, 1,2,3-thiadiazolyl, 1,2,3-triazolyl, 1,3-dioxo-isoindolyl, 1*H*-indolyl, 1*H*-pyrrolyl, 2,3-dihydro-1-oxo-isoindolyl, 2,3-dihydro-benzo[1,4]dioxinyl, 2*H*-benzopyranyl, 2-oxo-benzopyranyl, 2-oxo-pyrrolidinyl, 4-oxo-benzopyranyl, 9*H*-xanthenyl, benzo[1,3]dioxolyl, benzo[2,1,3]oxadiazolyl, benzo[1,2,5]oxadiazolyl, benzo[b]thienyl, furyl, isoxazolyl, morpholinyl, oxazolyl, pyrazolyl, pyridyl, pyrimidyl, pyrrolidyl, quinolyl, quinoxalyl, thiazolyl, thienyl, imidazolyl, or piperazyl;

halogen is fluoro, chloro, bromo, or iodo;

or a pharmaceutically acceptable salt, hydrate, or solvate thereof.

In some embodiments, compounds of the present invention are of Formula (I)

wherein R_2 is halogen, C_{1-5} alkyl, C_{1-5} alkoxy, $-N(R_{2a})(R_{2b})$, or heterocyclyl; wherein R_{2a} and R_{2b} are each independently hydrogen, C_{1-5} alkyl, C_{1-5} alkyl substituted by hydroxy, C_{1-5} alkyl substituted by carbocyclic aryl, C_{1-5} alkyl substituted by heterocyclyl, C_{3-6} cycloalkyl, or carbocyclic aryl; L is selected from the group consisting of Formulae (IIIa) and (IVa);

wherein R_3 and R_4 are each independently hydrogen or C_{1-5} alkyl; and A and B are each independently a single bond, $-CH_2-$, or $-(CH_2)_2-$; Z_1 is hydrogen, halogen, C_{1-5} alkyl, C_{1-5} alkyl substituted by halogen, C_{1-5} alkoxy, or C_{1-5} alkylthio; Z_2 is hydrogen, halogen, or C_{1-5} alkyl; or R_2 and Z_2 are bonded to each other to form a ring and $-R_2-Z_2-$ is $-NR_6-CH=CH-$; wherein R_6 is hydrogen or C_{1-5} alkyl; and Y represents:

(i) $-C(O)NR_5-$, $-C(S)NR_5-$, $-C(O)O-$, $-S(O)_2-$, $-C(O)-$, or $-(CH_2)_m-$ when L is selected from the group consisting of Formula (IIIa); or

(ii) $-C(O)NR_5-$ or $-C(O)O-$ when L is selected from the group consisting of Formula (IVa);

wherein R_5 is hydrogen or C_{1-5} alkyl; and m is 0, 1, or 2;

or a pharmaceutically acceptable salt, hydrate, or solvate thereof.

In some embodiments, compounds of the present invention are of Formula (I) wherein R_1 is selected from the group consisting of:

(i) C_{1-5} alkyl substituted by substituent(s) independly selected from the group consisting of:

•hydroxy,

•carbocyclic aryl,

•carbocyclic aryl substituted by halogen, and

•C_{1-5} alkylthio,

(ii) C_{3-6} cycloalkyl, and

(iii) carbocyclic aryl, and

carbocyclic aryl substituted by substituent(s) independly selected from the group consisting of:

•halogen,

•nitro,

•cyano,

•C_{1-5} alkyl,

•C_{1-5} alkyl substituted by halogen,

•C_{1-5} alkoxy,

•C_{1-5} alkoxy substituted by halogen,

•C_{1-5} alkoxy substituted by carbocyclic aryl,

•carbocyclic aryloxy, and

•carbocyclic aryloxy substituted by C_{1-5} alkoxy,

(iv) heterocyclyl, and

heterocyclyl substituted by substituent(s) independly selected from the group consisting of:

•halogen,

•C_{1-5} alkyl,

•carbocyclic aryl, and

•carbocyclic aryl substituted by halogen;

R_2 is $-N(R_{2a})(R_{2b})$ or heterocyclyl; wherein R_{2a} and R_{2b} are each independently hydrogen or C_{1-5} alkyl;

Z_1 is hydrogen, C_{1-5} alkyl, or C_{1-5} alkylthio; Z_2 is hydrogen or C_{1-5} alkyl; or R_2 and Z_2 are bonded to each other to form a ring and $-R_2-Z_2-$ is $-NR_6-CH=CH-$; wherein R_6 is hydrogen or C_{1-5} alkyl;

L is Formula (IIIa) or (IVa), wherein R_3 and R_4 are hydrogen, A is a single bond and B is a single bond or $-CH_2-$;

and

Y represents:

(i) -C(O)NH-, -C(S)NH, -C(O)-, or $-CH_2-$ when L is selected from the group consisting of Formula (IIIa); or

(ii) -C(O)NH- when L is selected from the group consisting of Formula (IVa);

wherein carbocyclic aryl is phenyl or naphthyl;

heterocyclyl is furyl, 1*H*-indolyl, morpholinyl, oxazolyl, piperidyl, pyridyl, pyrrolidyl, or 9*H*-xanthenyl;

halogen is fluoro, chloro, or bromo;

or a pharmaceutically acceptable salt, hydrate, or solvate thereof.

In some embodiments, compounds of the present invention are of Formula (I) wherein R_1 is selected from the group consisting of:

(i) carbocyclic aryl, and

carbocyclic aryl substituted by substituent(s) independly selected from the group consisting of:

•halogen,

•C_{1-5} alkyl,

•C_{1-5} alkyl substituted by halogen,

•C_{1-5} alkoxy, and

•C_{1-5} alkoxy substituted by halogen,

(ii) heterocyclyl, and

heterocyclyl substituted by halogen;

and

Z_1 is hydrogen, C_{1-5} alkyl, or C_{1-5} alkylthio; Z_2 is hydrogen or C_{1-5} alkyl;

wherein carbocyclic aryl is phenyl;

heterocyclyl is furyl, pyridyl, or pyrrolidyl;

halogen is fluoro, chloro, or bromo;

or a pharmaceutically acceptable salt, hydrate, or solvate thereof.

In some embodiments, compounds of the present invention are of Formula (I)

wherein the compound is selected from the group consisting of:

N-(*cis*-4-{[6-(dimethylamino)pyrimidin-4-yl]amino}cyclohexyl)-3,4-difluorobenzamide;

N-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-4-fluorobenzamide;

4-chloro-*N*-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-3-fluorobenzamide;

N-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-3,5-difluorobenzamide;

3-chloro-*N*-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-4-(trifluoromethoxy)benzamide;

3-chloro-4-fluoro-*N*-(*cis*-4-{[2-methyl-6-(methylamino)pyrimidin-4-yl]amino}cyclohexyl)benzamide;

N-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-3-fluorobenzamide;

4-chloro-*N*-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)benzamide;

N-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-3-fluoro-5-(trifluoromethyl)benzamide;

N-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-3,5-bis(trifluoromethyl)benzamide;

3-chloro-4-fluoro-*N*-{*cis*-4-[(2-methyl-6-piperidin-1-ylpyrimidin-4-yl)amino]cyclohexyl}benzamide;

3-chloro-4-fluoro-*N*-{*cis*-4-[(2-methyl-6-morpholin-4-ylpyrimidin-4-yl)amino]cyclohexyl}benzamide;

3-chloro-4-fluoro-*N*-{*cis*-4-[(7-methyl-7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)amino]cyclohexyl}benzamide;

3,4,5-trifluoro-*N*-{*cis*-4-[(7-methyl-7*H*-pyrrolo[2,3-d]pyrimidin-4-

yl)amino]cyclohexyl}benzamide;

3,4,5-trifluoro-*N*-(*cis*-4-{[2-methyl-6-(methylamino)pyrimidin-4-yl]amino}cyclohexyl)benzamide;

cis-*N*-(3,4-difluorophenyl)-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexanecarboxamide;

1-(4-chlorophenyl)-*N*-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)cyclopentanecarboxamide;

3-(2-chloro-6-fluorophenyl)-*N*-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-5-methylisoxazole-4-carboxamide;

N-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-(4-methoxyphenoxy)-5-nitrobenzamide;

N-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-5-iodo-2-furamide;

N-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-(ethylthio)-2,2-diphenylacetamide;

N-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-9*H*-xanthene-9-carboxamide;

N-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-*N*'-[1-(1-naphthyl)ethyl]urea;

N-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-*N*'-(3,4,5-trimethoxyphenyl)urea;

N-(5-chloro-2,4-dimethoxyphenyl)-*N*'-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)urea;

N-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-*N*'-(2,4,6-tribromophenyl)urea;

N-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-*N*'-mesitylthiourea;

N-(2,6-diethylphenyl)-*N*'-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-

yl]amino}cyclohexyl)thiourea;

N-(2,4-dichloro-6-methylphenyl)-*N'*-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)thiourea;

N-(5-chloro-2,4-dimethoxyphenyl)-*N'*-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)thiourea;

N-[4-bromo-2-(trifluoromethyl)phenyl]-*N'*-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)thiourea;

N-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-3-nitrobenzamide;

N-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3,4-diethoxy-benzamide;

N-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3-ethoxy-benzamide;

N-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3,5-diethoxy-benzamide;

N-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3-isopropoxy-benzamide;

3-bromo-*N*-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-4-fluoro-benzamide;

4-difluoromethoxy-*N*-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-benzamide;

4-chloro-*N*-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3-methyl-benzamide;

3-difluoromethoxy-*N*-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-benzamide;

3-chloro-*N*-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-4-methyl-benzamide;

4-bromo-*N*-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-

benzamide;

N-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3,5-dimethoxy-benzamide;

4-cyano-*N*-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-benzamide;

N-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-4-methoxy-benzamide;

3-cyano-*N*-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-benzamide;

N-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3-methoxy-benzamide;

N-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-4-fluoro-3-methyl-benzamide;

4-bromo-*N*-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3-methyl-benzamide;

N-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3-fluoro-4-methyl-benzamide;

N-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3-ethyl-benzamide;

3-bromo-*N*-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-benzamide;

N-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3-fluoro-4-trifluoromethyl-benzamide;

N-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-4-trifluoromethoxy-benzamide;

N-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-4-methyl-benzamide;

N-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3-methyl-

benzamide;

N-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-4-trifluoromethyl-benzamide;

2,2-difluoro-benzo[1,3]dioxole-5-carboxylic acid[*cis*-4-(6-dimethylamino- 2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-amide;

N-{*cis*-4-[(1*H*-indol-2-ylmethyl)-amino]-cyclohexyl}-2,*N'*,*N'*-trimethyl-pyrimidine-4,6-diamine;

2,*N*,*N*-trimethyl-*N'*-[*cis*-4-(3-trifluoromethoxy-benzylamino)-cyclohexyl]-pyrimidine-4,6-diamine;

N-[*cis*-4-(3,4-difluoro-benzylamino)-cyclohexyl]-2,*N'*,*N'*-trimethyl- pyrimidine-4,6-diamine;

1-(3,4-dimethoxy-phenyl)-3-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-urea;

1-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3-(2-ethoxy-phenyl)-urea;

1-(4-benzyloxy-phenyl)-3-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-urea;

3,5-dibromo-*N*-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-benzamide;

3-bromo-4-chloro-*N*-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-benzamide;

4-chloro-*N*-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3-trifluoromethyl-benzamide;

2-(3,5-bis-trifluoromethyl-phenyl)-*N*-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-2-hydroxy-acetamide;

N-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-3-fluoro-4-trifluoromethyl-benzamide;

N-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-3-

trifluoromethoxy-benzamide;

N-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-3-methoxy-benzamide;

4-chloro-*N*-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-benzamide;

N-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-3-trifluoromethyl-benzamide;

N-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-4-trifluoromethyl-benzamide;

N-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-3-methyl-benzamide;

N-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-3,5-difluoro-benzamide;

N-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-3-ethyl-benzamide;

2,2-difluoro-benzo[1,3]dioxole-5-carboxylic acid [*cis*-4-(6-dimethylamino- 2-methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-amide;

N-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-3-fluoro-4-methyl-benzamide;

N-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-4-fluoro-benzamide;

3,4-dichloro-*N*-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-benzamide;

4-bromo-*N*-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-benzamide;

N-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-3,4-difluoro-benzamide;

3,5-dichloro-*N*-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-

cyclohexylmethyl]-benzamide;

3-chloro-*N*-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-4-fluoro-benzamide;

N-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-4-fluoro-3-methyl-benzamide; and

3-chloro-*N*-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-benzamide;

or a pharmaceutically acceptable salt, hydrate, or solvate thereof.

In some embodiments, compounds of the present invention are of Formula (I) wherein the compound is selected from the group consisting of:

N-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-3,4-difluorobenzamide;

N-(*cis*-4-{[6-(dimethylamino)-2-ethylpyrimidin-4-yl]amino}cyclohexyl)-3,4-difluorobenzamide;

3-chloro-*N*-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-4-fluorobenzamide;

3,4-dichloro-*N*-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)benzamide;

3-chloro-*N*-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-5-fluorobenzamide;

N-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-3,4,5-trifluorobenzamide;

5-bromo-*N*-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)nicotinamide;

N-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-4-fluoro-3-(trifluoromethyl)benzamide;

N-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-3-(trifluoromethyl)benzamide;

N-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-3-(trifluoromethoxy)benzamide;

3,5-dichloro-*N*-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)benzamide;

3-chloro-*N*-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)benzamide;

3-chloro-4-fluoro-*N*-{*cis*-4-[(2-methyl-6-pyrrolidin-1-ylpyrimidin-4-yl)amino]cyclohexyl}benzamide;

N-(*cis*-4-{[6-(dimethylamino)-2-ethylpyrimidin-4-yl]amino}cyclohexyl)-3,4,5-trifluorobenzamide;

cis-*N*-(3-chloro-4-fluorophenyl)-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexanecarboxamide;

N-(*cis*-4-{[2-benzyl-6-(dimethylamino)pyrimidin-4-yl]amino}cyclohexyl)-3-chloro-4-fluorobenzamide;

cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}-*N*-(3,4,5-trifluorophenyl)cyclohexanecarboxamide;

N-(4-bromo-2,6-dimethylphenyl)-*N'*-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)urea;

N-(4-bromo-2,6-dimethylphenyl)-*N'*-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)thiourea;

N-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-*N'*-(3,4,5-trimethoxyphenyl)thiourea;

N-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-*N'*-(2,4,6-tribromophenyl)thiourea;

5-bromo-furan-2-carboxylic acid [*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-amide;

N-[*cis*-4-(3,5-dimethoxy-benzylamino)-cyclohexyl]-2,*N'*,*N'*-trimethyl-pyrimidine-4,6-diamine;

N-[*cis*-4-(3-bromo-benzylamino)-cyclohexyl]-2,*N'*,*N'*-trimethyl-pyrimidine-4,6-diamine;

1-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3-(3-methoxy- phenyl)-urea;

1-(3,5-difluoro-phenyl)-3-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)- cyclohexyl]-urea;

N-[*cis*-4-(6-dimethylamino-2-methylsulfanyl-pyrimidin-4-ylamino)-cyclohexyl]-3,4-difluoro-benzamide;

N-[*cis*-4-(6-dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3,4-difluoro-benzamide;

N-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-3,5-bis-trifluoromethyl-benzamide; and

N-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-4-trifluoromethoxy-benzamide;

or a pharmaceutically acceptable salt, hydrate, or solvate thereof.

In some embodiments, compounds of the present invention are of Formula (I) wherein R_1 represents:

(i) hydrogen, $-CO_2{}^tBu$, or $-CO_2Bn$ (Bn is a benzyl group) when L is selected from the group consisting of Formulae (III), (IIIa), and (IIIb); or

(ii) hydrogen, C_{1-5} alkyl, substituted C_{1-5} alkyl, Bn, or substituted Bn when L is selected from the group consisting of Formulae (IV), (IVa), and (IVb);

wherein R_3 and R_4 are each independently hydrogen or C_{1-5} alkyl; and A and B are each independently a single bond, $-CH_2-$, or $-(CH_2)_2-$; R_2 is halogen, C_{1-5} alkyl, C_{1-5} alkoxy, $-N(R_{2a})(R_{2b})$, or heterocyclyl; wherein R_{2a} and R_{2b} are each independently hydrogen, C_{1-5} alkyl, C_{1-5} alkyl substituted by hydroxy, C_{1-5} alkyl substituted by carbocyclic aryl, C_{1-5} alkyl substituted by heterocyclyl, C_{3-6} cycloalkyl, or carbocyclic aryl; Z_1 is hydrogen,

halogen, C_{1-5} alkyl, C_{1-5} alkyl substituted by halogen, C_{1-5} alkoxy, or C_{1-5} alkylthio; Z_2 is hydrogen, halogen, or C_{1-5} alkyl; or R_2 and Z_2 are bonded to each other to form a ring and -R_2-Z_2- is –NR_6-CH=CH-; wherein R_6 is hydrogen or C_{1-5} alkyl; and Y represents:

(i) a single bond when L is selected from the group consisting of Formulae (III), (IIIa), and (IIIb); or

(ii) -C(O)O- when L is selected from the group consisting of Formulae (IV), (IVa), and (IVb);

or a pharmaceutically acceptable salt, hydrate, or solvate thereof.

In some embodiments, compounds of the present invention are of Formula (I) wherein R_1 represents:

(i) hydrogen, -$CO_2{}^t$Bu, or -CO_2Bn (Bn is a benzyl group) when L is selected from the group consisting of Formula (IIIa); or

(ii) hydrogen, C_{1-5} alkyl, substituted C_{1-5} alkyl, Bn, or substituted Bn when L is selected from the group consisting of Formula (IVa);

wherein R_3 and R_4 are each hydrogen; and A and B are each independently a single bond or -CH_2-; R_2 is -$N(R_{2a})(R_{2b})$ or heterocyclyl; wherein R_{2a} and R_{2b} are each independently hydrogen or C_{1-5} alkyl; Z_1 is hydrogen, C_{1-5} alkyl, or C_{1-5} alkylthio; Z_2 is hydrogen or C_{1-5} alkyl; or R_2 and Z_2 are bonded to each other to form a ring and -R_2-Z_2- is –NR_6-CH=CH-; wherein R_6 is hydrogen or C_{1-5} alkyl; and Y represents:

(i) a single bond when L is selected from the group consisting of Formula (IIIa); or

(ii) -C(O)O- when L is selected from the group consisting of Formula (IVa);

heterocyclyl is furyl, 1*H*-indolyl, morpholinyl, oxazolyl, piperidyl, pyridyl, pyrrolidyl, or 9*H*-xanthenyl;

or a pharmaceutically acceptable salt, hydrate, or solvate thereof.

In some embodiments, compounds of the present invention are of Formula (I) wherein Q is Formula (IIb); R_2 is C_{1-5} alkyl substituted by hydroxy, C_{1-5} alkyl substituted

by carbocyclic aryl, C_{1-5} alkyl substituted by halogenated carbocyclic aryl, C_{1-5} alkyl substituted by heterocyclyl, C_{1-5} alkyl substituted by halogenated heterocyclyl, C_{2-5} alkenyl, C_{2-5} alkynyl, or $-N(R_{2a})(R_{2b})$; wherein R_{2a} and R_{2b} are each independently hydrogen, C_{1-5} alkyl, or C_{1-5} alkyl substituted by substituent(s) independently selected from the group consisting of:

- halogen,
- hydroxy,
- carboxy,
- carbamoyl,
- C_{1-5} alkoxy,
- amino,
- C_{3-6} cycloalkyl,
- carbocyclic aryl,
- carbocyclic aryl substituted by substituent(s) independently selected from the group consisting of:
  - halogen,
  - C_{1-5} alkyl,
  - C_{1-5} alkoxy,
  - C_{1-5} alkyl substituted by halogen,
  - C_{1-5} alkoxy substituted by halogen, and
  - $-SO_2NH_2$,
- heterocyclyl, and
- heterocyclyl substituted by substituent(s) independently selected from the group consisting of:
  - halogen,
  - C_{1-5} alkyl,
  - C_{1-5} alkoxy,
  - C_{1-5} alkyl substituted by halogen, and

••C_{1-5} alkoxy substituted by halogen,

carbocyclic aryl, carbocyclic aryl substituted by substituent(s) independently selected from the group consisting of:

•halogen,

•C_{1-5} alkyl,

•C_{1-5} alkoxy,

•C_{1-5} alkyl substituted by halogen, and

•C_{1-5} alkoxy substituted by halogen,

heterocyclyl, or heterocyclyl substituted by substituent(s) independently selected from the group consisting of:

•halogen,

•C_{1-5} alkyl,

•C_{1-5} alkoxy,

•C_{1-5} alkyl substituted by halogen, and

•C_{1-5} alkoxy substituted by halogen;

or a pharmaceutically acceptable salt, hydrate, or solvate thereof.

In some embodiments, compounds of the present invention are of Formula (I) wherein R_1 is selected from the group consisting of:

(i) C_{1-10} alkyl, and

C_{1-10} alkyl substituted by substituent(s) independently selected from the group consisting of:

•halogen,

•hydroxy,

•oxo,

•C_{1-5} alkoxy,

•C_{1-5} alkoxy substituted by carbocyclic aryl,

•C_{1-5} alkylcarbonyloxy,

•C_{1-5} alkoxycarbonyl,

•C_{1-5} alkoxycarbonyl substituted by carbocyclic aryl,

•carbocyclic aryloxy, and

•carbocyclic aryloxy substituted by substituent(s) independently selected from the group consisting of:

••halogen,

••nitro,

••C_{1-5} alkyl, and

••C_{1-5} alkyl substituted by oxo,

•heterocyclyloxy,

•heterocyclyloxy substituted by C_{1-5} alkyl,

•mono-carbocyclic arylamino,

•di-carbocyclic arylamino,

•carbocyclic arylsulfonylamino,

•carbocyclic arylsulfonylamino substituted by C_{1-5} alkyl,

•C_{1-5} alkylthio,

•C_{1-5} alkylthio substituted by carbocyclic aryl,

•carbocyclic arylthio,

•carbocyclic arylthio substituted by halogen,

•carbocyclic arylthio substituted by C_{1-5} alkyl,

•carbocyclic arylsulfonyl,

•carbocyclic arylsulfonyl substituted by halogen,

•heterocyclylthio,

•heterocyclylthio substituted by C_{1-5} alkyl,

•C_{3-6} cycloalkyl,

•C_{3-6} cycloalkenyl,

•carbocyclyl,

•carbocyclyl substituted by C_{1-5} alkoxy,

•carbocyclic aryl, and

•carbocyclic aryl substituted by substituent(s) independently selected from the group consisting of:

••halogen,

••nitro,

••C_{1-5} alkyl, and

••C_{1-5} alkyl substituted by substituent(s) independently selected from the group consisting of:

•••halogen,

•••carbocyclic aryl, and

•••heterocyclyl,

••C_{1-5} alkoxy,

••C_{1-5} alkoxy substituted by halogen,

••C_{1-5} alkoxy substituted by carbocyclic aryl,

••carbocyclic aryloxy,

••mono-carbocyclic arylaminocarbonyl, and

••mono-carbocyclic arylaminocarbonyl substituted by substituent(s) selected from the group consisting of:

•••halogen,

•••C_{1-5} alkyl,

•••C_{1-5} alkoxy, and

•••C_{1-5} alkoxy substituted by halogen,

••di-carbocyclic arylaminocarbonyl, and

••di-carbocyclic arylaminocarbonyl substituted by substituent(s) selected from the group consisting of:

•••halogen,

•••C_{1-5} alkyl,

•••C_{1-5} alkoxy, and

•••C_{1-5} alkoxy substituted by halogen,

••C_{1-5} alkylthio,

••C_{1-5} alkylthio substituted by halogen,

••C_{1-5} alkylsulfonyl,

••carbocyclic aryl, and

••heterocyclyl,

•heterocyclyl, and

•heterocyclyl substituted by substituent(s) independently selected from the group consisting of:

••C_{1-5} alkyl,

••C_{1-5} alkoxy,

••C_{1-5} alkoxy substituted by carbocyclic aryl,

••carbocyclic aryl, and

••carbocyclic aryl substituted by halogen,

(ii) C_{2-5} alkenyl, and

C_{2-5} alkenyl substituted by substituent(s) independently selected from the group consisting of:

•carbocyclic aryl, and

•carbocyclic aryl substituted by substituent(s) independently selected from the group consisting of:

••nitro,

••halogen,

••C_{1-5} alkyl,

••C_{1-5} alkyl substituted by halogen,

••C_{1-5} alkoxy, and

••C_{1-5} alkoxy substituted by halogen,

(iii) C_{3-6} cycloalkyl, and

C_{3-6} cycloalkyl substituted by substituent(s) independently selected from the group consisting of:

•C_{1-5} alkyl,

•C_{1-5} alkyl substituted by carbocyclic aryl,

•carbocyclic arylcarbonylamino, and

•carbocyclic aryl,

(iv) carbocyclyl, and

carbocyclyl substituted by nitro,

(v) carbocyclic aryl, and

carbocyclic aryl substituted by substituent(s) independently selected from the group consisting of:

•halogen,

•cyano,

•nitro,

•C_{1-9} alkyl, and

•C_{1-9} alkyl substituted by substituent(s) independently selected from the group consisting of:

••halogen,

••oxo,

••mono-carbocyclic arylaminocarbonyl,

••di-carbocyclic arylaminocarbonyl,

••mono-carbocyclic arylaminocarbonyl substituted by C_{1-5} alkoxy,

••di-carbocyclic arylaminocarbonyl substituted by C_{1-5} alkoxy,

••carbocyclic aryoxy,

••carbocyclic aryl, and

••carbocyclic aryl substituted by substituent(s) independently selected from the group consisting of:

•••halogen,

•••C_{1-5} alkyl, and

•••C_{1-5} alkyl substituted by halogen,

••heterocyclyl, and

••heterocyclyl substituted by C_{1-5} alkyl,

•C_{2-5} alkenyl,

•C_{1-7} alkoxy,

•C_{1-7} alkoxy substituted by halogen,

•C_{1-7} alkoxy substituted by carbocyclic aryl,

•C_{3-6} cycloalkoxy,

•carbocyclic aryloxy, and

•carbocyclic aryloxy substituted by substituent(s) independently selected from the group consisting of:

••halogen,

••nitro, and

••C_{1-5} alkoxy

•heterocyclyloxy, and

•heterocyclyloxy substituted by substituent(s) independently selected from the group consisting of:

••halogen,

••C_{1-5} alkyl, and

••C_{1-5} alkyl substituted by halogen,

•C_{1-5} alkoxycarbonyl,

•mono-C_{1-5} alkylaminocarbonyl,

•di-C_{1-5} alkylaminocarbonyl,

•mono-C_{1-5} alkylaminocarbonyl substituted by carbocyclic aryl,

•di-C_{1-5} alkylaminocarbonyl substituted by carbocyclic aryl,

•mono-carbocyclic arylaminocarbonyl,

•di-carbocyclic arylaminocarbonyl,

•mono-carbocyclic arylaminocarbonyl substituted by C_{1-5} alkyl,

•di-carbocyclic arylaminocarbonyl substituted by C_{1-5} alkyl,

•mono-C_{1-5} alkylamino,

•di-C_{1-5} alkylamino,

•C_{1-5} alkylthio,

•C_{1-5} alkylthio substituted by halogen,

•C_{1-5} alkylsulfonyl,

•carbocyclic aryl, and

•carbocyclic aryl substituted by substituent(s) independently selected from the group consisting of:

••C_{1-7} alkyl, and

••C_{1-7} alkyl substituted by halogen,

(vi) heterocyclyl, and

heterocyclyl substituted by substituent(s) independently selected from the group consisting of:

•halogen,

•C_{1-5} alkyl, and

•C_{1-5} alkyl substituted by substituent(s) independently selected from the group consisting of:

••halogen,

••oxo,

••carbocyclic aryl,

••carbocyclic aryl substituted by halogen,

••heterocyclyl, and

••heterocyclyl substituted by substituent(s) independently selected from the group consisting of:

•••halogen,

•••C_{1-5} alkyl, and

•••C_{1-5} alkyl substituted by halogen,

•C_{1-5} alkoxy,

•C_{1-5} alkylthio,

•carbocyclic arylthio,

•C_{1-5} alkylsulfonyl,

•carbocyclic arylsulfonyl,

•carbocyclic arylsulfonyl substituted by halogen,

•carbocyclic arylsulfonyl substituted by C_{1-5} alkyl,

•C_{1-5} alkoxycarbonyl,

•carbocyclic aryl, and

•carbocyclic aryl substituted by substituent(s) independently selected from the group consisting of:

••halogen,

••nitro, and

••C_{1-5} alkyl,

•heterocyclyl, and

•heterocyclyl substituted by substituent(s) independently selected from the group consisting of:

••halogen,

••C_{1-5} alkyl, and

••C_{1-5} alkyl substituted by halogen;

wherein carbocyclic aryl is phenyl, naphthyl, or anthranyl;

carbocyclyl is 1-oxo-indanyl, 9*H*-fluorenyl, 9-oxo-fluorenyl, anthraquinonyl, *C*-fluoren-9-ylidene, indanyl, or menthyl;

heterocyclyl is 1,2,3,4-tetrahydro-isoquinolyl, 1,2,3-thiadiazolyl, 1,2,3-triazolyl, 1,3-dioxo-isoindolyl, 1*H*-indolyl, 1*H*-pyrrolyl, 2,3-dihydro-1-oxo-isoindolyl, 2,3-dihydro-benzo[1,4]dioxinyl, 2*H*-

benzopyranyl, 2-oxo-benzopyranyl, 2-oxo-pyrrolidinyl, 4-oxo-benzopyranyl, 9*H*-xanthenyl, benzo[1,3]dioxolyl, benzo[2,1,3]oxadiazolyl, benzo[1,2,5]oxadiazolyl, benzo[b]thienyl, furyl, isoxazolyl, morpholinyl, oxazolyl, pyrazolyl, pyridyl, pyrimidyl, pyrrolidyl, quinolyl, quinoxalyl, thiazolyl, or thienyl;

halogen is fluoro, chloro, bromo, or iodo;

or a pharmaceutically acceptable salt, hydrate, or solvate thereof.

In some embodiments, compounds of the present invention are of Formula (I) wherein R_2 is C_{1-5} alkyl substituted by carbocyclic aryl, C_{1-5} alkyl substituted by halogenated carbocyclic aryl, C_{1-5} alkyl substituted by heterocyclyl, C_{1-5} alkyl substituted by halogenated heterocyclyl, carbocyclic aryl, carbocyclic aryl by halogen, heterocyclyl, heterocyclyl by halogen, or $-N(R_{2a})(R_{2b})$; wherein R_{2a} and R_{2b} are each independently hydrogen, C_{1-5} alkyl, C_{1-5} alkyl substituted by hydroxy, or C_{1-5} alkyl substituted by halaogen; L is Formula (IIIa); wherein R_3 and R_4 are each independently hydrogen or C_{1-5} alkyl; and A and B are each independently a single bond, $-CH_2-$, or $-(CH_2)_2-$; Z_3 and Z_4 are each independently hydrogen, halogen, C_{1-5} alkyl, C_{1-5} alkyl substituted by halogen, mono-C_{1-5} alkyl amino, or di-C_{1-5} alkyl amino; and Y is $-C(O)-$, $-C(O)NR_5-$, $-C(S)NR_5-$, or $-(CH_2)_m-$; wherein R_5 is hydrogen or C_{1-5} alkyl; and m is 0, 1, or 2; Y is not $-(CH_2)_m-$ provided that either R_{2a} or R_{2b} is hydrogen;

or a pharmaceutically acceptable salt, hydrate, or solvate thereof.

In some embodiments, compounds of the present invention are of Formula (I) wherein R_1 is selected from the group consisting of:

(i) C_{1-5} alkyl substituted by substituent(s) independly selected from the group consisting of:

•hydroxy,

•carbocyclic aryl,

•carbocyclic aryl substituted by halogen, and

•carbocyclic aryl substituted by halogenated C_{1-5} alkyl,

(ii) carbocyclic aryl, and

carbocyclic aryl substituted by substituent(s) independly selected from the group consisting of:

•halogen,

•cyano,

•C_{1-5} alkyl,

•C_{1-5} alkyl substituted by halogen,

•C_{1-5} alkoxy, and

•C_{1-5} alkoxy substituted by halogen,

(iii) heterocyclyl, and

heterocyclyl substituted by halogen;

R_2 is C_{1-5} alkyl substituted by carbocyclic aryl or $-N(R_{2a})(R_{2b})$; wherein R_{2a} and R_{2b} are each independently hydrogen or C_{1-5} alkyl;

L is Formula (IIIa); wherein R_3 and R_4 are each hydrogen; and A and B are each a single bond;

Z_3 and Z_4 are each independently hydrogen, C_{1-5} alkyl, mono-C_{1-5} alkyl amino, or di-C_{1-5} alkyl amino;

and

Y is -C(O)-;

wherein carbocyclic aryl is phenyl;

heterocyclyl is furyl or pyridyl;

halogen is fluoro, chloro, or bromo;

or a pharmaceutically acceptable salt, hydrate, or solvate thereof.

In some embodiments, compounds of the present invention are of Formula (I) wherein R_1 is selected from the group consisting of:

carbocyclic aryl, and

carbocyclic aryl substituted by substituent(s) independly selected from the

group consisting of:

•halogen,

•cyano, and

•C_{1-5} alkoxy;

Z_3 is hydrogen when Z_4 is C_{1-5} alkyl; or Z_3 is C_{1-5} alkyl, mono-C_{1-5} alkyl amino, or di-C_{1-5} alkyl amino when Z_4 is hydrogen;

or a pharmaceutically acceptable salt, hydrate, or solvate thereof.

In some embodiments, compounds of the present invention are of Formula (I) wherein the compound is selected from the group consisting of:

3-chloro-*N*-(*cis*-4-{[2-(dimethylamino)-6-methylpyrimidin-4-yl]amino}cyclohexyl)-4-fluorobenzamide;

N-(*cis*-4-{[2-(dimethylamino)-6-methylpyrimidin-4-yl]amino}cyclohexyl)-3,4-difluorobenzamide;

N-[*cis*-4-(2-dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3-methoxy-benzamide;

N-[*cis*-4-(2-dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3-trifluoromethyl-benzamide;

N-[*cis*-4-(2-dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3,5-bis-trifluoromethyl-benzamide;

2,2-difluoro-benzo[1,3]dioxole-5-carboxylic acid [*cis*-4-(2-dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-amide;

4-cyano-*N*-[*cis*-4-(2-dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-benzamide;

4-chloro-*N*-[*cis*-4-(2-dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-benzamide;

N-[*cis*-4-(2-dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3-ethyl-benzamide;

N-[*cis*-4-(2-dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3,4-difluoro-benzamide;

5-bromo-*N*-[*cis*-4-(2-dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-nicotinamide;

5-bromo-furan-2-carboxylic acid [*cis*-4-(2-dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-amide;

3,5-dibromo-*N*-[*cis*-4-(2-dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-benzamide;

N-[*cis*-4-(2-dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3-ethoxy-benzamide;

2-(3,5-bis-trifluoromethyl-phenyl)-*N*-[*cis*-4-(2-dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-2-hydroxy-acetamide;

2-(4-bromo-phenyl)-*N*-[*cis*-4-(2-dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-2-hydroxy-acetamide;

N-[*cis*-4-(2-dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3,5-diethoxy-benzamide;

3-bromo-*N*-[*cis*-4-(2-dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-4-fluoro-benzamide;

N-[*cis*-4-(2-dimethylamino-6-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3-ethoxy-benzamide;

N-[*cis*-4-(2-dimethylamino-6-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3-trifluoromethyl-benzamide;

N-[*cis*-4-(2-dimethylamino-6-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3,5-bis-trifluoromethyl-benzamide;

2,2-difluoro-benzo[1,3]dioxole-5-carboxylic acid [*cis*-4-(2-dimethylamino-6-methyl-pyrimidin-4-ylamino)-cyclohexyl]-amide;

4-chloro-*N*-[*cis*-4-(2-dimethylamino-6-methyl-pyrimidin-4-ylamino)-cyclohexyl]-benzamide;

N-[*cis*-4-(2-dimethylamino-6-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3-ethyl-benzamide;

N-[*cis*-4-(2-dimethylamino-6-methyl-pyrimidin-4-ylamino)-cyclohexyl]-4-methyl-benzamide;

5-bromo-*N*-[*cis*-4-(2-dimethylamino-6-methyl-pyrimidin-4-ylamino)-cyclohexyl]-nicotinamide;

5-bromo-furan-2-carboxylic acid [*cis*-4-(2-dimethylamino- 6-methyl-pyrimidin-4-ylamino)-cyclohexyl]-amide;

3,5-dibromo-*N*-[*cis*-4-(2-dimethylamino-6-methyl-pyrimidin-4-ylamino)-cyclohexyl]-benzamide;

N-[*cis*-4-(2-dimethylamino-6-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3-ethoxy-benzamide;

2-(3,5-bis-trifluoromethyl-phenyl)-*N*-[*cis*-4-(2-dimethylamino-6-methyl-pyrimidin-4-ylamino)-cyclohexyl]-2-hydroxy-acetamide;

2-(4-bromo-phenyl)-*N*-[*cis*-4-(2-dimethylamino-6-methyl-pyrimidin-4-ylamino)-cyclohexyl]-2-hydroxy-acetamide;

N-[*cis*-4-(2-dimethylamino-6-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3,5-diethoxy-benzamide; and

3-bromo-*N*-[*cis*-4-(2-dimethylamino-6-methyl-pyrimidin-4-ylamino)-cyclohexyl]-4-fluoro-benzamide;

or a pharmaceutically acceptable salt, hydrate, or solvate thereof.

In some embodiments, compounds of the present invention are of Formula (I) wherein the compound is selected from the group consisting of:

3-chloro-*N*-(*cis*-4-{[2-(dimethylamino)pyrimidin-4-yl]amino}cyclohexyl)-4-fluorobenzamide;

N-(*cis*-4-{[2,6-bis(dimethylamino)pyrimidin-4-yl]amino}cyclohexyl)-3,4-difluorobenzamide;

N-(*cis*-4-{[2-benzyl-6-(dimethylamino)pyrimidin-4-yl]amino}cyclohexyl)-3-

chloro-4-fluorobenzamide;

3,4-dichloro-*N*-[*cis*-4-(2-dimethylamino-6-methyl-pyrimidin-4-ylamino)-cyclohexyl]-benzamide;

4-cyano-*N*-[*cis*-4-(2-dimethylamino-6-methyl-pyrimidin-4-ylamino)-cyclohexyl]-benzamide;

N-[*cis*-4-(2-dimethylamino-6-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3,4-diethoxy-benzamide;

3-chloro-*N*-[*cis*-4-(2-dimethylamino-6-methyl-pyrimidin-4-ylamino)-cyclohexyl]-5-fluoro-benzamide;

N-[*cis*-4-(2-dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3,5-dimethoxy-benzamide;

3,4-dichloro-*N*-[*cis*-4-(2-dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-benzamide;

N-[*cis*-4-(2-dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3,4-diethoxy-benzamide; and

3-chloro-*N*-[*cis*-4-(2-dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-5-fluoro-benzamide;

or a pharmaceutically acceptable salt, hydrate, or solvate thereof.

In some embodiments, compounds of the present invention are of Formula (I) wherein R_1 is selected from hydrogen, $-CO_2{}^tBu$, or $-CO_2Bn$ (Bn is a benzyl group); R_2 is C_{1-5} alkyl substituted by carbocyclic aryl, C_{1-5} alkyl substituted by halogenated carbocyclic aryl, C_{1-5} alkyl substituted by heterocyclyl, C_{1-5} alkyl substituted by halogenated heterocyclyl, carbocyclic aryl, carbocyclic aryl by halogen, heterocyclyl, heterocyclyl by halogen, or $-N(R_{2a})(R_{2b})$; wherein R_{2a} and R_{2b} are each independently hydrogen, C_{1-5} alkyl, C_{1-5} alkyl substituted by hydroxy, or C_{1-5} alkyl substituted by halaogen; L is Formula (IIIa); wherein R_3 and R_4 are each independently hydrogen or C_{1-5} alkyl; and A and B are each independently a single bond, $-CH_2-$, or $-(CH_2)_2-$; Z_3 and Z_4 are each independently hydrogen, halogen, C_{1-5} alkyl, C_{1-5} alkyl substituted by halogen, mono-C_{1-5} alkyl amino, or

di-C_{1-5} alkyl amino; and Y is a single bond;

or a pharmaceutically acceptable salt, hydrate, or solvate thereof.

In some embodiments, compounds of the present invention are of Formula (I) wherein R_2 is C_{1-5} alkyl substituted by carbocyclic aryl or $-N(R_{2a})(R_{2b})$; wherein R_{2a} and R_{2b} are each independently hydrogen or C_{1-5} alkyl; L is Formula (IIIa); wherein R_3 and R_4 are each hydrogen; and A and B are each a single bond; and Z_3 and Z_4 are each independently hydrogen, C_{1-5} alkyl, mono-C_{1-5} alkyl amino, or di-C_{1-5} alkyl amino;

wherein carbocyclic aryl is phenyl;

heterocyclyl is furyl or pyridyl;

halogen is fluoro, chloro, or bromo;

or a pharmaceutically acceptable salt, hydrate, or solvate thereof.

One aspect of the present invention pertains to pharmaceutical compositions comprising a therapeutically effective amount of at least one compound, as described herein, in combination with a pharmaceutically acceptable carrier.

One aspect of the present invention pertains to methods for the prophylaxis or treatment of improving memory function, sleeping and arousal, anxiety, depression, mood disorders, seizure, obesity, diabetes, appetite and eating disorders, cardiovascular disease, hypertension, dyslipidemia, myocardial infarction, binge eating disorders including bulimia, anorexia, mental disorders including manic depression, schizophrenia, delirium, dementia, stress, cognitive disorders, attention deficit disorder, substance abuse disorders and dyskinesias including Parkinson's disease, epilepsy, and addiction comprising administering to an individual suffering from the condition a therapeutically effective amount of a compound, as described herein, or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for the prophylaxis or treatment of an eating disorder, obesity or an obesity related disorder comprising administering to an individual suffering from the condition a therapeutically effective amount of a compound, as described herein, or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for the prophylaxis or

treatment of anxiety, depression, schizophrenia, addiction, or epilepsy comprising administering to an individual suffering from the condition a therapeutically effective amount of a compound, as described herein, or a pharmaceutical composition.

One aspect of the present invention pertains to compounds of the present invention, as described herein, or a pharmaceutical composition thereof, for use in a method of treatment of the human or animal body by therapy.

One aspect of the present invention pertains to compounds of the present invention, as described herein, or a pharmaceutical composition thereof, for use in a method of prophylaxis or treatment of an eating disorder, obesity or an obesity related disorder of the human or animal body by therapy.

One aspect of the present invention pertains to compounds of the present invention, as described herein, or a pharmaceutical composition thereof, for use in a method of prophylaxis or treatment of anxiety, depression, schizophrenia, addiction, or epilepsy of the human or animal body by therapy.

One aspect of the present invention pertains to compounds of the present invention, as described herein, for the manufacture of a medicament for use in the prophylaxis or treatment of an eating disorder, obesity or obesity related disorders.

One aspect of the present invention pertains to compounds of the present invention, as described herein, for the manufacture of a medicament for use in the prophylaxis or treatment of anxiety, depression, schizophrenia, addiction, or epilepsy.

One aspect of the present invention pertains to methods of decreasing food intake of an individual comprising administering to the individual a therapeutically effective amount of a compound, as described herein, or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods of inducing satiety in an individual comprising administering to said individual a therapeutically effective amount of a compound, as described herein, or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods of controlling or reducing weight gain in an individual comprising administering to said individual a therapeutically

effective amount of a compound, as described herein, or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods of modulating a MCH receptor in an individual comprising contacting the receptor with a compound, as described herein. In some embodiments, the compound is an antagonist. In some embodiments, the modulation of the MCH receptor is for the prophylaxis or treatment of an eating disorder, obesity or obesity related disorder. In some embodiments, the modulation of the MCH receptor reduces food intake of the individual. In some embodiments, the modulation of the MCH receptor induces satiety in the individual. In some embodiments, the modulation of the MCH receptor controls or reduces weight gain of the individual. In some embodiments, the modulation of the MCH receptor is for prophylaxis or treatment of anxiety, depression, schizophrenia, addiction, or epilepsy.

In some embodiments, the individual is a mammal.

In some embodiments, the mammal is a human.

In some embodiments, the human has a body mass index of about 18.5 to about 45. In some embodiments, the human has a body mass index of about 25 to about 45. In some embodiments, the human has a body mass index of about 30 to about 45. In some embodiments, the human has a body mass index of about 35 to about 45.

One aspect of the present invention pertains to methods of producing a pharmaceutical composition comprising admixing a compound, as described herein, and a pharmaceutically acceptable carrier.

One embodiment of the invention includes any compound of the invention which selectively binds an MCH receptor, such selective binding is preferably demonstrated by a Ki for one or more other GPCR(s), preferably NPY, being at least 10-fold greater than the Ki for any particular MCH receptor, preferable MCHR1.

As used herein, the term "alkyl" is intended to denote hydrocarbon compounds including straight chain and branched chain, including for example but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, tert-

pentyl, n-hexyl, and the like.

The term "alkoxy" is intended to denote substituents of the formula -O-alkyl.

At various places in the present specification substituents of compounds of the invention are disclosed in groups. It is specifically intended that the invention include each and every individual subcombination of the members of such groups.

G-protein coupled receptors (GPCRs) represent a major class of cell surface receptors with which many neurotransmitters interact to mediate their effects. GPCRs are predicted to have seven membrane-spanning domains and are coupled to their effectors via G-proteins linking receptor activation with intracellular biochemical sequelae such as stimulation of adenylyl cyclase. Melanin Concentrating Hormone (MCH), a cyclic peptide, has been identified as the endogenous ligand of the orphan G-protein coupled receptor SLC-1. See, for example, Shimomura et al., Biochem. Biophys. Res. Commun. 261, 622-26 (1999). Studies have indicated that MCH acts as a neurotransmitter/modulator/regulator to alter a number of behavioral responses.

Mammalian MCH (19 amino acids) is highly conserved between rat, mouse, and human, exhibiting 100% amino acid identity, but its physiological roles are less clear. MCH has been reported to participate in a variety of processes including feeding, water balance, energy metabolism, general arousal/attention state, memory and cognitive functions, and psychiatric disorders. For reviews, see 1. Baker, Int. Rev. Cytol. 126:1-47 (1991); 2. Baker, TEM 5:120-126 (1994); 3. Nahon, Critical Rev. in Neurobiol 221:221-262, (1994); 4. Knigge et al., Peptides 18(7):1095–1097, (1996). The role of MCH in feeding or body weight regulation is supported by Qu et al., Nature 380:243-247, (1996), demonstrating that MCH is over expressed in the hypothalamus of ob/ob mice compared with ob/+mice, and that fasting further increased MCH mRNA in both obese and normal mice during fasting. MCH also stimulated feeding in normal rats when injected into the lateral ventricles as reported by Rossi et al., Endocrinology 138:351-355, (1997). MCH also has been reported to functionally antagonize the behavioral effects of α-MSH; see:

Miller et al., Peptides 14:1-10, (1993); Gonzalez et al, Peptides 17:171-177, (1996); and Sanchez et al., Peptides 18:3933-396, (1997). In addition, stress has been shown to increase POMC mRNA levels while decreasing the MCH precursor preproMCH (ppMCH) mRNA levels; Presse et al., Endocrinology 131:1241-1250, (1992). Thus MCH can serve as an integrative neuropeptide involved in the reaction to stress, as well as in the regulation of feeding and sexual activity; Baker, Int. Rev. Cytol. 126:1-47, (1991); Knigge et al., Peptides 17:1063-1073, (1996).

The localization and biological activities of MCH peptide suggest that the modulation of MCH receptor activity can be useful in a number of therapeutic applications. MCH is expressed in the lateral hypothalamus, a brain area implicated in the regulation of thirst and hunger: Grillon et al., Neuropeptides 31:131-136, (1997); recently orexins A and B, which are potent orexigenic agents, have been shown to have very similar localization to MCH in the lateral hypothalamus; Sakurai et al., Cell 92:573-585 (1998). MCH mRNA levels in this brain region are increased in rats after 24 hours of food-deprivation; Herve and Fellmann, Neurpeptides 31:237-242 (1997); after insulin injection, a significant increase in the abundance and staining intensity of MCH immunoreactive perikarya and fibres was observed concurrent with a significant increase in the level of MCH mRNA; Bahjaoui-Bouhaddi et al., Neuropeptides 24:251-258, (1994). Consistent with the ability of MCH to stimulate feeding in rats; Rossi et al., Endocrinology 138:351-355, (1997); is the observation that MCH mRNA levels are upregulated in the hypothalami of obese ob/ob mice; Qu et al., Nature 380:243-247, (1996); and decreased in the hypothalami of rats treated with leptin, whose food intake and body weight gains are also decreased; Sahu, Endocrinology 139:795-798, (1998). MCH appears to act as a functional antagonist of the melanocortin system in its effects on food intake and on hormone secretion within the HPA (hypothalamopituitary/adrenal axis); Ludwig et al., Am. J. Physiol. Endocrinol. Metab. 274:E627-E633, (1998). Together these data suggest a role for endogenous MCH in the regulation of energy balance and response to stress, and provide a rationale for the development of specific compounds acting at MCH receptors for use in the treatment of

obesity and stress-related disorders.

Accordingly, a MCH receptor antagonist is desirable for the prophylaxis or treatment of obesity or obesity related disorders. An obesity related disorder is a disorder that has been directly or indirectly associated to obesity, such as, type II diabetes, syndrome X, impaired glucose tolerance, dyslipidaemia, hypertension, coronary heart disease and other cardiovascular disorders including atherosclerosis, insulin resistance associated with obesity and psoriasis, for treating diabetic complications and other diseases such as polycystic ovarian syndrome (PCOS), certain renal diseases including diabetic nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis, end-stage renal diseases and microalbuminuria as well as certain eating disorders.

In species studied to date, a major portion of the neurons of the MCH cell group occupies a rather constant location in those areas of the lateral hypothalamus and subthalamus where they lie and may be a part of some of the so-called "extrapyramidal" motor circuits. These involve substantial striato- and pallidofugal pathways involving the thalamus and cerebral cortex, hypothalamic areas, and reciprocal connections to subthalamic nucleus, substantia nigra, and mid-brain centers; Bittencourt et al., J. Comp. Neurol. 319:218-245, (1992). In their location, the MCH cell group may offer a bridge or mechanism for expressing hypothalamic visceral activity with appropriate and coordinated motor activity. Clinically it can be of some value to consider the involvement of this MCH system in movement disorders, such as Parkinson's disease and Huntingdon's Chorea in which extrapyramidal circuits are known to be involved.

Human genetic linkage studies have located authentic hMCH loci on chromosome 12 (12q23-24) and the variant hMCH loci on chromosome 5 (5q12-13) (Pedeutour et al., 1994). Locus 12q23-24 coincides with a locus to which autosomal dominant cerebellar ataxia type II (SCA2) has been mapped; Auburger et al., Cytogenet. Cell. Genet. 61:252-256, (1992); Twells et al., Cytogenet. Cell. Genet. 61:262-265, (1992). This disease comprises neurodegenerative disorders, including an olivopontocerebellar atrophy.

Furthermore, the gene for Darier's disease, has been mapped to locus 12q23-24; Craddock et al., Hum. Mol. Genet. 2:1941-1943, (1993). Dariers' disease is characterized by abnormalities I keratinocyte adhesion and mental illnesses in some families. In view of the functional and neuroanatomical patterns of the MCH neural system in the rat and human brains, the MCH gene can represent a good candidate for SCA2 or Darier's disease. Interestingly, diseases with high social impact have been mapped to this locus. Indeed, the gene responsible for chronic or acute forms of spinal muscular atrophies has been assigned to chromosome 5q12-13 using genetic linkage analysis; Melki et al., Nature (London) 344:767-768, (1990); Westbrook et al., Cytogenet. Cell. Genet. 61:225-231, (1992). Furthermore, independent lines of evidence support the assignment of a major schizophrenia locus to chromosome 5q11.2-13.3; Sherrington et al., Nature (London) 336:164-167, (1988); Bassett et al., Lancet 1:799-801, (1988); Gilliam et al., Genomics 5:940-944, (1989). The above studies suggest that MCH can play a role in neurodegenerative diseases and disorders of emotion.

Additional therapeutic applications for MCH-related compounds are suggested by the observed effects of MCH in other biological systems. For example, MCH can regulate reproductive functions in male and female rats. MCH transcripts and MCH peptide were found within germ cells in testes of adult rats, suggesting that MCH can participate in stem cell renewal and/or differentiation of early spermatocytes; Hervieu et al., Biology of Reduction 54:1161-1172, (1996). MCH injected directly into the medial preoptic area (MPOA) or ventromedial nucleus (VMN) stimulated sexual activity in female rats; Gonzalez et al., Peptides 17:171-177, (1996). In ovariectomized rats primed with estradiol, MCH stimulated luteinizing hormone (LH) release while anti-MCH antiserum inhibited LH release; Gonzalez et al., Neuroendocrinology 66:254-262, (1997). The zona incerta, which contains a large population of MCH cell bodies, has previously been identified as a regulatory site for the pre-ovulatory LH surge; MacKenzie et al., Neuroendocrinology 39:289-295, (1984). MCH has been reported to influence release of pituitary hormones including ACTH and oxytocin. MCH analogues can also be useful in treating epilepsy. In

the PTZ seizure model, injection of MCH prior to seizure induction prevented seizure activity in both rats and guinea pigs, suggesting that MCH-containing neurons can participate in the neural circuitry underlying PTZ-induced seizure; Knigge and Wagner, Peptides 18:1095-1097, (1997). MCH has also been observed to affect behavioral correlates of cognitive functions. MCH treatment hastened extinction of the passive avoidance response in rats; McBride et al., Peptides 15:757-759, (1994); raising the possibility that MCH receptor antagonists can be beneficial for memory storage and/or retention. A possible role for MCH in the modulation or perception of pain is supported by the dense innervation of the periaqueductal grey (PAG) by MCH-positive fibers. Finally, MCH can participate in the regulation of fluid intake. ICV infusion of MCH in conscious sheep produced diuretic, natriuretic, and kaliuretic changes in response to increased plasma volume; Parkes, J. Neuroendocrinol. 8:57-63, (1996). Together with anatomical data reporting the presence of MCH in fluid regulatory areas of the brain, the results indicate that MCH can be an important peptide involved in the central control of fluid homeostasis in mammals.

In a recent citation MCHR1 antagonists surprisingly demonstrated their use as an anti-depressants and/or anti-anxiety agents. MCHR1 antagonists have been reported to show antidepressant and anxiolytic activities in rodent models, such as, social interaction, forced swimming test and ultrasonic vocalization. Therefore, MCHR1 antagonists could be useful to independently treat subjects with depression and/or anxiety. Also, MCHR1 antagonists could be useful to treat subjects that suffer from depression and/or anxiety and obesity.

This invention provides a method of treating an abnormality in a subject wherein the abnormality is alleviated by decreasing the activity of a mammalian MCH1 receptor which comprises administering to the subject an amount of a compound which is a mammalian MCH1 receptor antagonist effective to treat the abnormality. In separate embodiments, the abnormality is a regulation of a steroid or pituitary hormone disorder, an epinephrine release disorder, an anxiety disorder, genta gastrointestinal disorder, a

cardiovascular disorder, an electrolyte balance disorder, hypertension, diabetes, a respiratory disorder, asthma, a reproductive function disorder, an immune disorder, an endocrine disorder, a musculoskeletal disorder, a neuroendocrine disorder, a cognitive disorder, a memory disorder, a sensory modulation and transmission disorder, a motor coordination disorder, a sensory integration disorder, a motor integration disorder, a dopaminergic function disorder, a sensory transmission disorder, an olfaction disorder, a sympathetic innervation disorder, an affective disorder, a stress-related disorder, a fluid-balance disorder, a seizure disorder, pain, psychotic behavior, morphine tolerance, opiate addiction or migraine.

Compositions of the invention can conveniently be administered in unit dosage form and can be prepared by any of the methods well known in the pharmaceutical art, for example, as described in *Remington's Pharmaceutical Sciences* (Mack Pub. Co., Easton, PA, 1980).

The compounds of the invention can be employed as the sole active agent in a pharmaceutical or can be used in combination with other active ingredients which could facilitate the therapeutic effect of the compound.

Compounds of the present invention or a solvate or physiologically functional derivative thereof can be used as active ingredients in pharmaceutical compositions, specifically as a MCH receptor antagonists. By the term "active ingredient" is defined in the context of a "pharmaceutical composition" and shall mean a component of a pharmaceutical composition that provides the primary pharmaceutical benefit, as opposed to an "inactive ingredient" which would generally be recognized as providing no pharmaceutical benefit. The term "pharmaceutical composition" shall mean a composition comprising at one active ingredient and at least one ingredient that is not an active ingredient (for example and not limitation, a filler, dye, or a mechanism for slow release), whereby the composition is amenable to use for a specified, efficacious outcome in a mammal (for example, and not limitation, a human).

Pharmaceutical compositions, including, but not limited to, pharmaceutical

compositions, comprising at least one compound of the present invention and/or an acceptable salt or solvate thereof (*e.g.*, a pharmaceutically acceptable salt or solvate) as an active ingredient combined with at least one carrier or excipient (*e.g.*, pharmaceutical carrier or excipient) can be used in the treatment of clinical conditions for which a MCH receptor antagonist is indicated. At least one compound of the present invention can be combined with the carrier in either solid or liquid form in a unit dose formulation. The pharmaceutical carrier must be compatible with the other ingredients in the composition and must be tolerated by the individual recipient. Other physiologically active ingredients can be incorporated into the pharmaceutical composition of the invention if desired, and if such ingredients are compatible with the other ingredients in the composition. Formulations can be prepared by any suitable method, typically by uniformly mixing the active compound(s) with liquids or finely divided solid carriers, or both, in the required proportions, and then, if necessary, forming the resulting mixture into a desired shape.

Conventional excipients, such as binding agents, fillers, acceptable wetting agents, tabletting lubricants, and disintegrants can be used in tablets and capsules for oral administration. Liquid preparations for oral administration can be in the form of solutions, emulsions, aqueous or oily suspensions, and syrups. Alternatively, the oral preparations can be in the form of dry powder that can be reconstituted with water or another suitable liquid vehicle before use. Additional additives such as suspending or emulsifying agents, non-aqueous vehicles (including edible oils), preservatives, and flavorings and colorants can be added to the liquid preparations. Parenteral dosage forms can be prepared by dissolving the compound of the invention in a suitable liquid vehicle and filter sterilizing the solution before filling and sealing an appropriate vial or ampoule. These are just a few examples of the many appropriate methods well known in the art for preparing dosage forms.

It is noted that when the MCH receptor antagonists are utilized as active ingredients in a pharmaceutical composition, these are not intended for use only in humans, but in other non-human mammals as well. Indeed, recent advances in the area of animal

health-care mandate that consideration be given for the use of MCH receptor antagonists for the treatment of obesity in domestic animals (*e.g.*, cats and dogs), and MCH receptor antagonists in other domestic animals where no disease or disorder is evident (*e.g.*, food-oriented animals such as cows, chickens, fish, etc.). Those of ordinary skill in the art are readily credited with understanding the utility of such compounds in such settings.

Pharmaceutically acceptable salts of the compounds of the invention can be prepared by reacting the free acid or base forms of these compounds with the appropriate base or acid in water, in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, dioxane, or acetonitrile are preferred. For instance, when the compound (I) possesses an acidic functional group, it can form an inorganic salt such as an alkali metal salt (e.g., sodium salt, potassium salt, etc.), an alkaline earth metal salt (e.g. calcium salt, magnesium salt, barium salt, etc.), and an ammonium salt. When the compound (I) possesses a basic functional group, it can form an inorganic salt (e.g., hydrochloride, sulfate, phosphate, hydrobromate, etc.) or an organic salt (e.g., acetate, maleate, fumarate, succinate, methanesulfonate, p-toluenesulfonate, citrate, tartrate, etc.).

When a compound of the invention contains optical isomers, stereoisomers, regio isomers, rotational isomers, a single substance and a mixture of them are included as a compound of the invention. For example, when a chemical formula is represented as showing no stereochemical designation(s), such as Formula (III), then all possible stereoisomer, optical isomers and mixtures thereof are considered within the scope of that formula. Accordingly, Formula (IIIa), specifically designates the cis relationship between the two amino groups on the cyclohexyl ring and therefore this formula is also fully embraced by Formula (III).

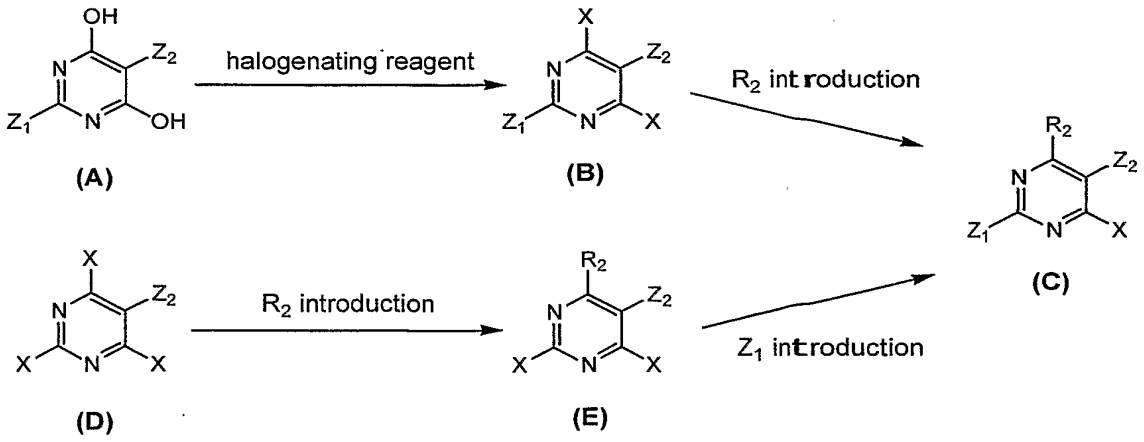
Preparation of Compound of Formula (I) - General synthetic methods

The novel substituted pyrimidines of the present invention can be readily prepared according to a variety of synthetic manipulations, all of which would be familiar to one

skilled in the art. Preferred methods for the preparation of compounds of the present invention include, but are not limited to, those described in Scheme 1-8.

The pyrimidine (C) can be prepared as shown in Scheme 1. 4,6-Dihydroxypyrimidine (A), which is commercially available or is condensed from malonic acid derivatives and amidine derivatives, wherein Z_1 and Z_2 are as defined above, is converted to 4,6-dihalo-pyrimidine (B) by a halogenating agent with or without a base (wherein X is halogen such as chloro, bromo, or iodo). The halogenating agent includes phosphorous oxychloride ($POCl_3$), phosphorous oxybromide ($POBr_3$), or phosphorus pentachloride (PCl_5). The base includes a tertiary amine (preferably *N,N*-diisopropylethylamine, etc.) or an aromatic amine (preferably *N,N*-dimethylaniline, etc.). Reaction temperature ranges from about 100 °C to 200 °C, preferably about 140 °C to 180 °C. The introduction of R_2 substituent to 4,6-dihalo-pyrimidine (B) gives the pyrimidine (C). Also the pyrimidine (C) can be prepared from commercially available 2,4,6-trihalo-pyrimidine (D), wherein Z_2 is as defined above and X is halogen such as chloro, bromo, or iodo, following the introduction of R_2 substituent and Z_1 substituent.

Scheme 1

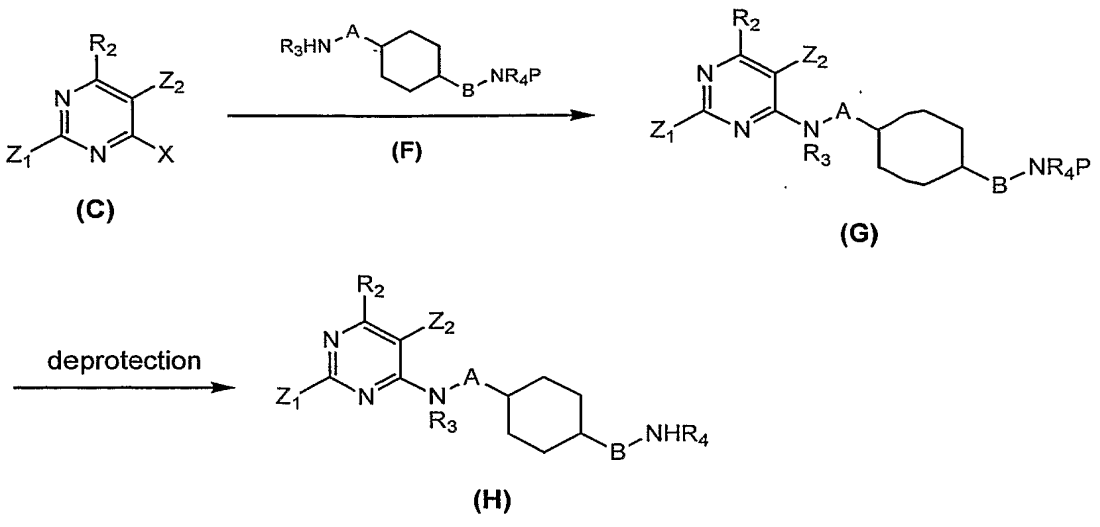


The common intermediate (H) of the novel substituted pyrimidines can be prepared as shown in Scheme 2. The pyrimidine (C) is substituted by the mono-protected

diamine (F), wherein R_3, R_4, A, and B are as defined above and P is a protective group, with or without a base in an inert solvent to provide the coupling adduct (G). The base includes an alkali metal carbonate (preferably sodium carbonate or potassium carbonate, etc.), an alkali metal hydroxide (preferably sodium hydroxide, etc.), or a tertiary amine (preferably *N,N*-diisopropylethylamine, triethylamine, or *N*-methylmorpholine, etc.). The inert solvent includes lower alkyl alcohol solvents (preferably methanol, ethanol, 2-propanol, or butanol, etc.) or amide solvents (preferably *N,N*-dimethylformamide or 1-methyl-pyrrolidin-2-one, etc.). Reaction temperature ranges from about 50 °C to 200 °C, preferably about 80 °C to 150 °C. Also this reaction can be carried out under microwave conditions.

Representative protecting groups suitable for a wide variety of synthetic transformations are disclosed in Greene and Wuts, *Protective Groups in Organic Synthesis*, second edition, John Wiley & Sons, New York, 1991, the disclosure of which is incorporated herein by reference in its entirety. The deprotection of the protective group leads to the common intermediate (H) of the novel substituted pyrimidines.

Scheme 2



The conversion of the common intermediate (H) to the novel substituted pyrimidines (I), (J), and (V)-(X) of the present invention is outlined in Scheme 3.

The amine (H) is reacted with a carboxylic acid (R_1CO_2H) and a dehydrating condensing agent in an inert solvent with or without a base to provide the novel amide (I) of the present invention. The dehydrating condensing agent includes dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC•HCl), bromo-tris-pyrrolidino-phosnium hexafluorophosphate (PyBroP), *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU), or 1-cyclohexyl-3-methylpolystyrene-carbodiimide. The base includes a tertiary amine (preferably *N*,*N*-diisopropylethylamine or triethylamine, etc.). The inert solvent includes lower halocarbon solvents (preferably dichloromethane, dichloroethane, or chloroform, etc.), ethereal solvents (preferably tetrahydrofuran or dioxane), nitrile solvents (preferably acetonitrile, etc.), or amide solvents (preferably *N*,*N*-dimethylformamide, etc.). In case of need, 1-hydroxybenzotriazole (HOBT), HOBT-6-carboxaamidomethyl polystyrene, or 1-hydroxy-7-azabenzotriazole (HOAT) can be used as a reactant agent. Reaction temperature ranges from about -20 °C to 50 °C, preferably about 0 °C to 40 °C.

Alternatively, the novel amide (I) of the present invention can be obtained by amidation reaction using an acid chloride (R_1COCl) and a base in an inert solvent. The base includes an alkali metal carbonate (preferably sodium carbonate or potassium carbonate, etc.), an alkali metal hydrogencarbonate (preferably sodium hydrogencarbonate or potassium hydrogencarbonate, etc.), an alkali hydroxide (preferably sodium hydroxide or potassium hydroxide, etc.), a tertiary amine (preferably *N*,*N*-diisopropylethylamine, triethylamine, or *N*-methylmorpholine, etc.), or an aromatic amine (preferably pyridine, imidazole, poly-(4-vinylpyridine), etc.). The inert solvent includes lower halocarbon solvents (preferably dichloromethane, dichloroethane, or chloroform, etc.), ethereal solvents (preferably tetrahydrofuran or dioxane), amide solvents (preferably *N*,*N*-dimethylformamide, etc.), or aromatic solvents (preferably toluene or pyridine, etc.). Reaction temperature ranges from about -20 °C to 50 °C, preferably about 0 °C to 40 °C.

The novel amide (I) of the present invention is reacted with a reducing agent in an inert solvent to provide the novel amine (J) of the present invention. The reducing agent

includes alkali metal aluminum hydrides (preferably lithium aluminum hydride), alkali metal borohydrides (preferably lithium borohydride), alkali metal trialkoxyaluminum hydrides (preferably lithium tri-*tert*-butoxyaluminum hydride), dialkylaluminum hydrides (preferably di-isobutylaluminum hydride), borane, dialkylboranes (preferably di-isoamyl borane), alkali metal trialkylboron hydrides (preferably lithium triethylboron hydride). The inert solvent includes ethereal solvents (preferably tetrahydrofuran or dioxane) or aromatic solvents (preferably toluene, etc.). Reaction temperature ranges from about -78 °C to 200 °C, preferably about 50 °C to 120 °C.

Alternatively, the novel amine (J) of the present invention can be obtained by reductive amination reaction using aldehyde (R_1CHO) and a reducing agent in an inert solvent with or without an acid. The reducing agent includes sodium triacetoxyborohydride, sodium cyanoborohydride, sodium borohydride, or boran-pyridine complex, preferably sodium triacetoxyborohydride or sodium cyanoborohydride. The inert solvent includes lower alkyl alcohol solvents (preferably methanol or ethanol, etc.), lower halocarbon solvents (preferably dichloromethane, dichloroethane, or chloroform, etc.), ethereal solvents (preferably tetrahydrofuran or dioxane), or aromatic solvents (preferably toluene, etc.). The acid includes an inorganic acid (preferably hydrochloric acid or sulfuric acid) or an organic acid (preferably acetic acid). Reaction temperature ranges from about -20 °C to 120 °C, preferably about 0 °C to 100 °C. Also this reaction can be carried out under microwave conditions.

The amine (I) is reacted with a sulfonyl halide (R_1SO_2X), wherein X is halogen such as chloro, bromo, or iodo, and a base in an inert solvent to provide the novel sulfonamide (V) of the present invention. The base includes an alkali metal carbonate (preferably sodium carbonate or potassium carbonate, etc.), an alkali metal hydrogencarbonate (preferably sodium hydrogencarbonate or potassium hydrogencarbonate, etc.), an alkali hydroxide (preferably sodium hydroxide or potassium hydroxide, etc.), a tertiary amine (preferably *N*,*N*-diisopropylethylamine, triethylamine, or *N*-methylmorpholine, etc.), or an aromatic amine (preferably pyridine or imidazole, etc.).

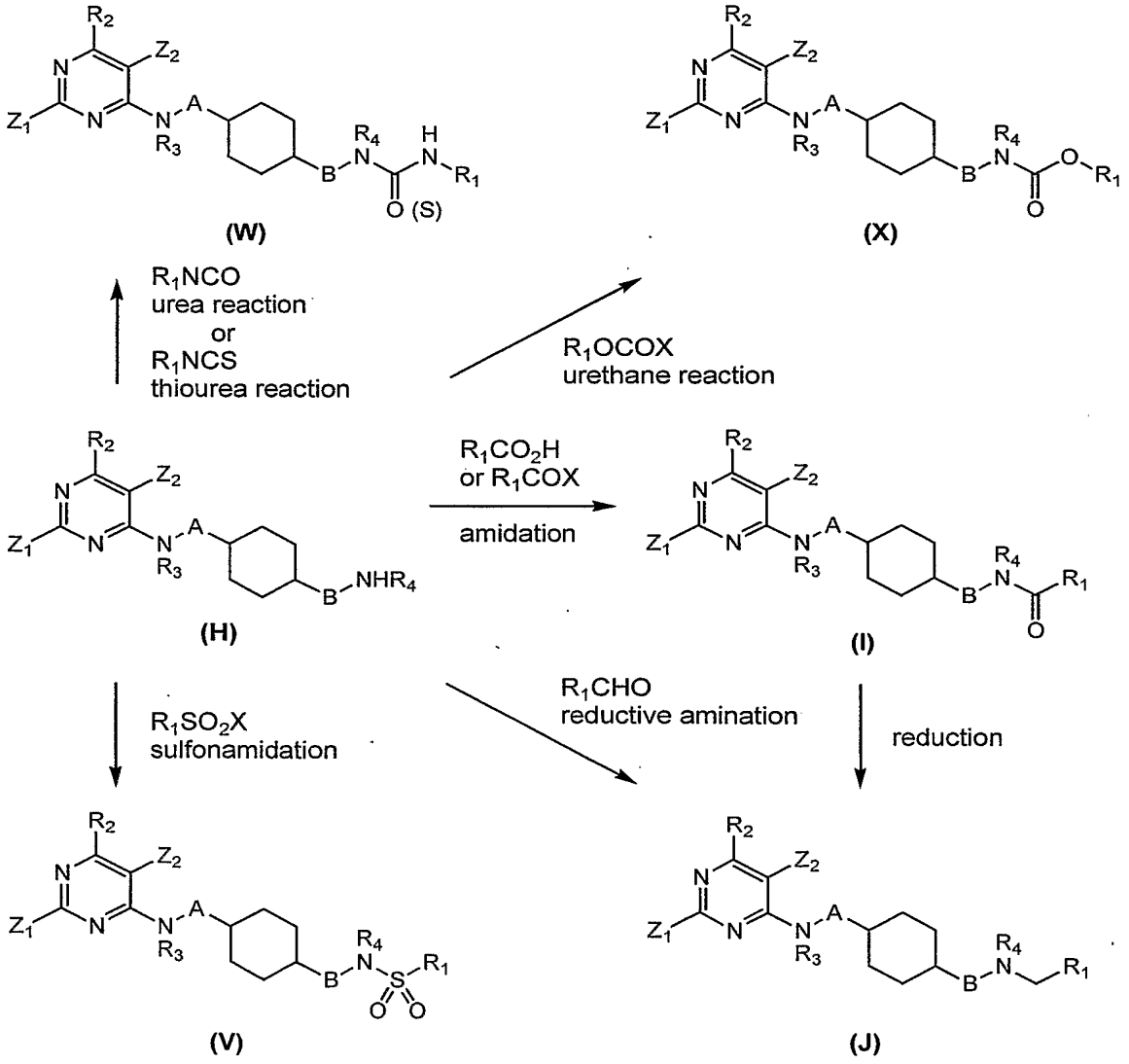
The inert solvent includes lower halocarbon solvents (preferably dichloromethane, dichloroethane, or chloroform, etc.), ethereal solvents (preferably tetrahydrofuran or dioxane), alcohol solvents (preferably 2-propanol, etc.), or aromatic solvents (preferably toluene or pyridine, etc.). Reaction temperature ranges from about -20 °C to 50 °C, preferably about 0 °C to 40 °C.

The novel urea (W) or thiourea (W) of the present invention can be obtained by urea reaction or thiourea reaction using an isocyanate (R_1NCO) or isothiocyanate (R_1NCS) in an inert solvent with or without a base. The base includes an alkali metal carbonate (preferably sodium carbonate or potassium carbonate, etc.), an alkali metal hydrogencarbonate (preferably sodium hydrogencarbonate or potassium hydrogencarbonate, etc.), an alkali hydroxide (preferably sodium hydroxide or potassium hydroxide, etc.), a tertiary amine (preferably *N*,*N*-diisopropylethylamine, triethylamine, or *N*-methylmorpholine, etc.), or an aromatic amine (preferably pyridine or imidazole, etc.). The inert solvent includes lower halocarbon solvents (preferably dichloromethane, dichloroethane, or chloroform, etc.), ethereal solvents (preferably tetrahydrofuran or dioxane), aromatic solvents (preferably benzene or toluene, etc.), or polar solvents (preferably *N*,*N*-dimethylformamide or dimethyl sulfoxide, etc.). Reaction temperature ranges from about -20 °C to 120 °C, preferably about 0 °C to 100 °C.

The novel urethane (X) of the present invention can be obtained by urethane reaction using R_1OCOX, wherein X is halogen such as chloro, bromo, or iodo, in an inert solvent with or without a base. The base includes an alkali metal carbonate (preferably sodium carbonate or potassium carbonate, etc.), an alkali metal hydrogencarbonate (preferably sodium hydrogencarbonate or potassium hydrogencarbonate, etc.), an alkali hydroxide (preferably sodium hydroxide or potassium hydroxide, etc.), a tertiary amine (preferably *N*,*N*-diisopropylethylamine, triethylamine, or *N*-methylmorpholine, etc.), or an aromatic amine (preferably pyridine, imidazole, or poly-(4-vinylpyridine), etc.). The inert solvent includes lower halocarbon solvents (preferably dichloromethane, dichloroethane, or chloroform, etc.), ethereal solvents (preferably tetrahydrofuran or dioxane), aromatic

solvents (preferably benzene or toluene, etc.), or polar solvents (preferably *N,N*-dimethylformamide or dimethyl sulfoxide, etc.). Reaction temperature ranges from about -20 °C to 120 °C, preferably about 0 °C to 100 °C.

Scheme 3

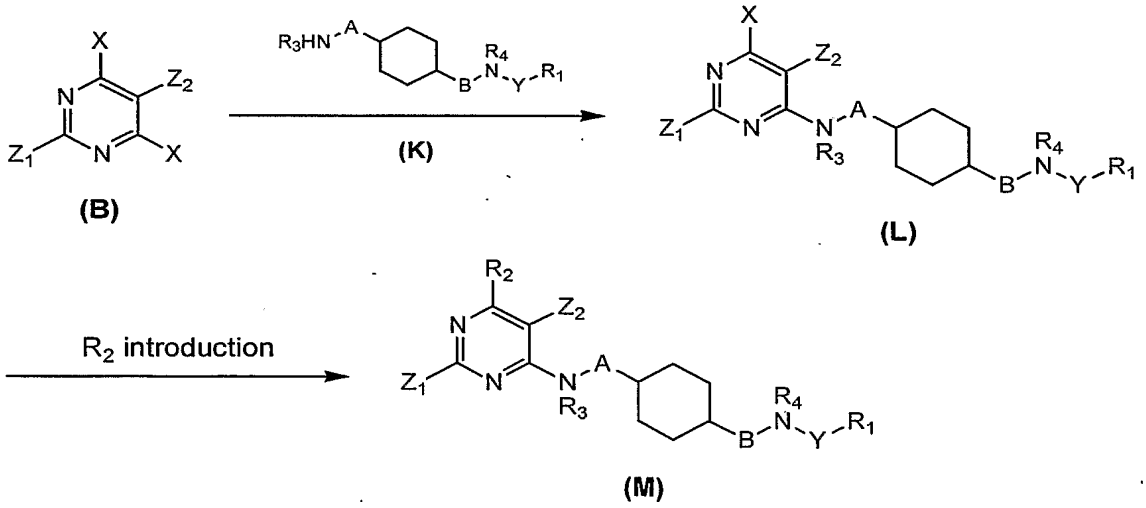


Also the novel substituted pyrimidine (M) of the present invention can be prepared as shown in Scheme 4.

First 4,6-dihalo-pyrimidine (B) is substituted by the amine (K) which has been

already installed by the desired R_1 substituent, wherein R_3, R_4, A, B, Y, and R_1 are as defined above, with or without a base in an inert solvent to provide the coupling adduct (L). The base includes an alkali metal carbonate (preferably sodium carbonate or potassium carbonate, etc.), an alkali metal hydroxide (preferably sodium hydroxide, etc.), or a tertiary amine (preferably *N*,*N*-diisopropylethylamine, triethylamine, or *N*-methylmorpholine, etc.). The inert solvent includes lower alkyl alcohol solvents (preferably methanol, ethanol, 2-propanol, or butanol, etc.) or amide solvents (preferably *N*,*N*-dimethylformamide or 1-methyl-pyrrolidin-2-one, etc.). Reaction temperature ranges from about 50 °C to 200 °C, preferably about 80 °C to 150 °C. Also this reaction can be carried out under microwave conditions. The introduction of R_2 substituent leads to the novel substituted pyrimidine (M) of the present invention.

Scheme 4



The common intermediate (R) of the novel substituted pyrimidines can be prepared as shown in Scheme 5.

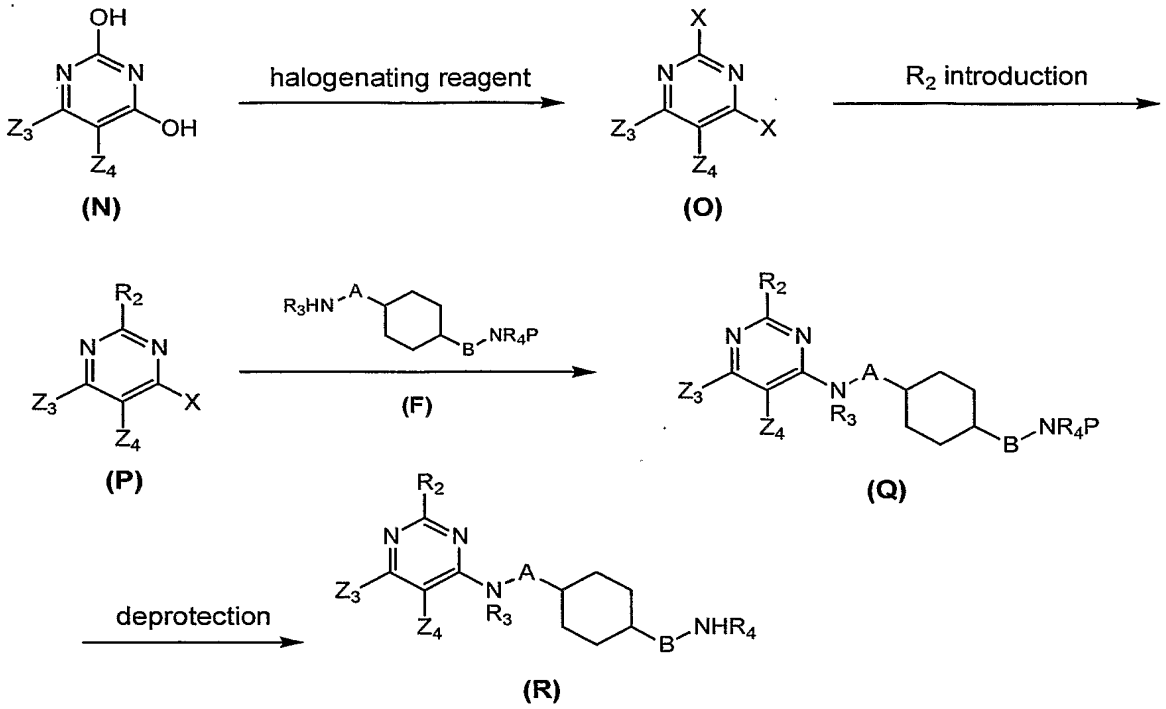
Commercially available 2,4-dihydroxypyrimidine (N) , wherein Z_3 and Z_4 are as defined above, is converted to 2,4-dihalo-pyrimidine (O) by a halogenating agent with or without a base (wherein X is halogen such as chloro, bromo, or iodo). The halogenating

agent includes phosphorous oxychloride ($POCl_3$), phosphorous oxybromide ($POBr_3$), or phosphorus pentachloride (PCl_5). The base includes a tertiary amine (preferably *N,N*-diisopropylethylamine, etc.) or an aromatic amine (preferably *N,N*-dimethylaniline, etc.). Reaction temperature ranges from about 100 °C to 200 °C, preferably about 140 °C to 180 °C. The introduction of R_2 substituent to 2,4-dihalo-pyrimidine (O) gives the pyrimidine (P). The pyrimidine (P) is substituted by the mono-protected diamine (F), wherein R_3, R_4, A, and B are as defined above and P is a protective group, with or without a base in an inert solvent to provide the coupling adduct (Q). The base includes an alkali metal carbonate (preferably sodium carbonate or potassium carbonate, etc.), an alkali metal hydroxide (preferably sodium hydroxide, etc.), or a tertiary amine (preferably *N,N*-diisopropylethylamine, triethylamine, or *N*-methylmorpholine, etc.). The inert solvent includes lower alkyl alcohol solvents (preferably methanol, ethanol, 2-propanol, or butanol, etc.) or amide solvents (preferably *N,N*-dimethylformamide or 1-methyl-pyrrolidin-2-one, etc.). Reaction temperature ranges from about 50 °C to 200 °C, preferably about 80 °C to 150 °C. Also this reaction can be carried out under microwave conditions.

It is understood that regioisomers can be formed using certain methods described herein, such as Scheme 5, and that these regioisomers could be separated by using methods known to one skilled in the art.

Representative protecting groups suitable for a wide variety of synthetic transformations are disclosed in Greene and Wuts, *Protective Groups in Organic Synthesis*, second edition, John Wiley & Sons, New York, 1991, the disclosure of which is incorporated herein by reference in its entirety. The deprotection of the protective group leads to the common intermediate (R) of the novel substituted pyrimidines.

Scheme 5



The conversion of the common intermediate (R) to the novel substituted pyrimidines (S), (T), and (V)-(A') of the present invention is outlined in Scheme 6.

The amine (R) is reacted with a carboxylic acid (R_1CO_2H) and a dehydrating condensing agent in an inert solvent with or without a base to provide the novel amide (S) of the present invention. The dehydrating condensing agent includes dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC•HCl), bromo-tris-pyrrolidino-phosnium hexafluorophosphate (PyBroP), *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU), or 1-cyclohexyl-3-methylpolystyrene-carbodiimide. The base includes a tertiary amine (preferably *N,N*-diisopropylethylamine or triethylamine, etc.). The inert solvent includes lower halocarbon solvents (preferably dichloromethane, dichloroethane, or chloroform, etc.), ethereal solvents (preferably tetrahydrofuran or dioxane), nitrile solvents (preferably acetonitrile, etc.), or amide solvents (preferably *N,N*-dimethylformamide, etc.). In case of need, 1-hydroxybenzotriazole (HOBT), HOBT-6-carboxaamidomethyl

polystyrene, or 1-hydroxy-7-azabenzotriazole (HOAT) can be used as a reactant agent. Reaction temperature ranges from about -20 °C to 50 °C, preferably about 0 °C to 40 °C.

Alternatively, the novel amide (S) of the present invention can be obtained by amidation reaction using an acid chloride (R_1COCl) and a base in an inert solvent. The base includes an alkali metal carbonate (preferably sodium carbonate or potassium carbonate, etc.), an alkali metal hydrogencarbonate (preferably sodium hydrogencarbonate or potassium hydrogencarbonate, etc.), an alkali hydroxide (preferably sodium hydroxide or potassium hydroxide, etc.), a tertiary amine (preferably *N*,*N*-diisopropylethylamine, triethylamine, or *N*-methylmorpholine, etc.), or an aromatic amine (preferably pyridine, imidazole, poly-(4-vinylpyridine), etc.). The inert solvent includes lower halocarbon solvents (preferably dichloromethane, dichloroethane, or chloroform, etc.), ethereal solvents (preferably tetrahydrofuran or dioxane), amide solvents (preferably *N*,*N*-dimethylformamide, etc.), or aromatic solvents (preferably toluene or pyridine, etc.). Reaction temperature ranges from about -20 °C to 50 °C, preferably about 0 °C to 40 °C.

The novel amide (S) of the present invention is reacted with a reducing agent in an inert solvent to provide the novel amine (T) of the present invention. The reducing agent includes alkali metal aluminum hydrides (preferably lithium aluminum hydride), alkali metal borohydrides (preferably lithium borohydride), alkali metal trialkoxyaluminum hydrides (preferably lithium tri-*tert*-butoxyaluminum hydride), dialkylaluminum hydrides (preferably di-isobutylaluminum hydride), borane, dialkylboranes (preferably di-isoamyl borane), alkali metal trialkylboron hydrides (preferably lithium triethylboron hydride). The inert solvent includes ethereal solvents (preferably tetrahydrofuran or dioxane) or aromatic solvents (preferably toluene, etc.). Reaction temperature ranges from about -78 °C to 200 °C, preferably about 50 °C to 120 °C.

Alternatively, the novel amine (T) of the present invention can be obtained by reductive amination reaction using aldehyde (R_1CHO) and a reducing agent in an inert solvent with or without an acid. The reducing agent includes sodium triacetoxyborohydride, sodium cyanoborohydride, sodium borohydride, or boran-pyridine

complex, preferably sodium triacetoxyborohydride or sodium cyanoborohydride. The inert solvent includes lower alkyl alcohol solvents (preferably methanol or ethanol, etc.), lower halocarbon solvents (preferably dichloromethane, dichloroethane, or chloroform, etc.), ethereal solvents (preferably tetrahydrofuran or dioxane), or aromatic solvents (preferably toluene, etc.). The acid includes an inorganic acid (preferably hydrochloric acid or sulfuric acid) or an organic acid (preferably acetic acid). Reaction temperature ranges from about -20 °C to 120 °C, preferably about 0 °C to 100 °C. Also this reaction can be carried out under microwave conditions.

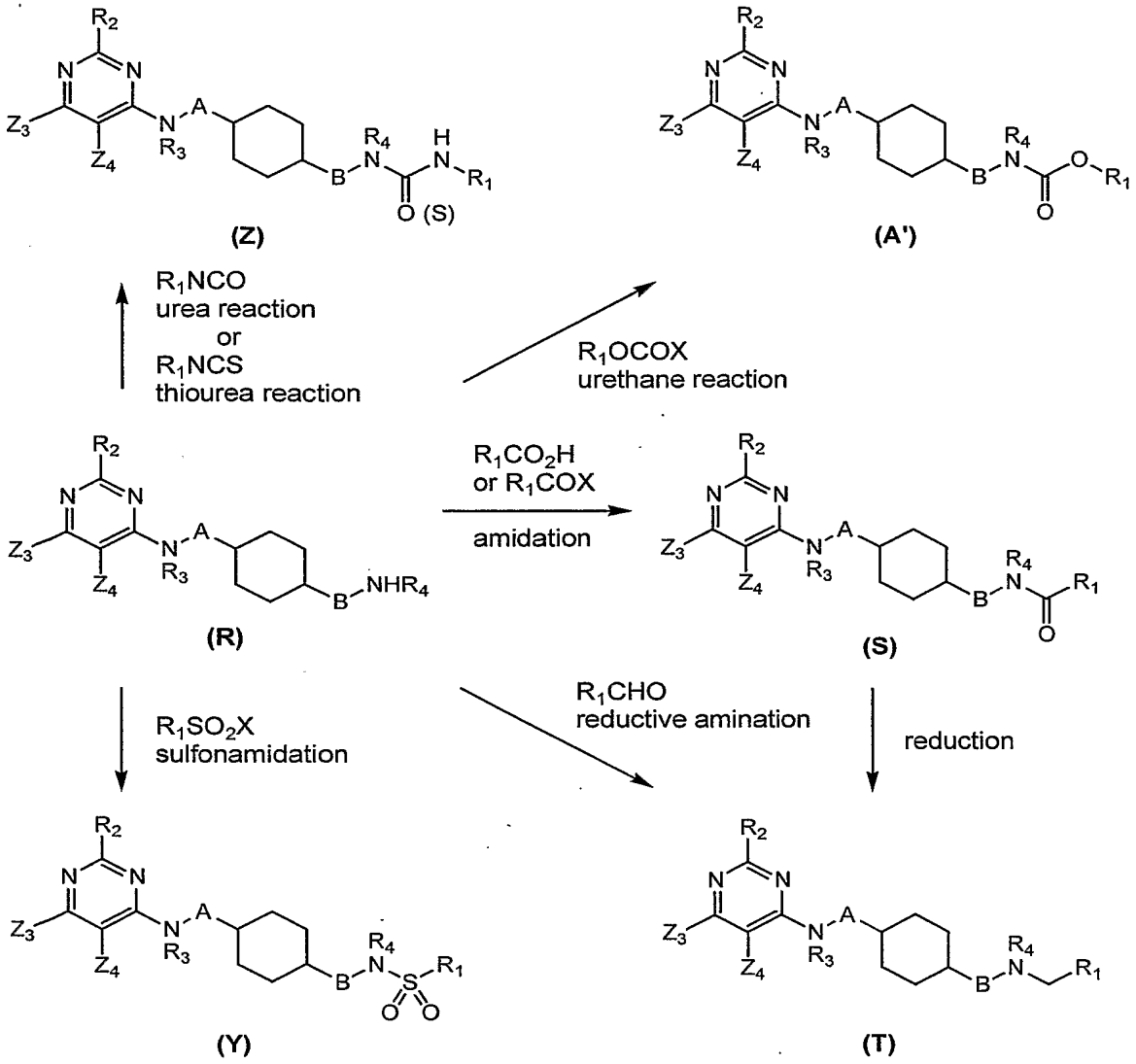
The amine (R) is reacted with a sulfonyl halide (R_1SO_2X), wherein X is halogen such as chloro, bromo, or iodo, and a base in an inert solvent to provide the novel sulfonamide (Y) of the present invention. The base includes an alkali metal carbonate (preferably sodium carbonate or potassium carbonate, etc.), an alkali metal hydrogencarbonate (preferably sodium hydrogencarbonate or potassium hydrogencarbonate, etc.), an alkali hydroxide (preferably sodium hydroxide or potassium hydroxide, etc.), a tertiary amine (preferably *N*,*N*-diisopropylethylamine, triethylamine, or *N*-methylmorpholine, etc.), or an aromatic amine (preferably pyridine or imidazole, etc.). The inert solvent includes lower halocarbon solvents (preferably dichloromethane, dichloroethane, or chloroform, etc.), ethereal solvents (preferably tetrahydrofuran or dioxane), alcohol solvents (preferably 2-propanol, etc.), or aromatic solvents (preferably toluene or pyridine, etc.). Reaction temperature ranges from about -20 °C to 50 °C, preferably about 0 °C to 40 °C.

The novel urea (Z) or thiourea (Z) of the present invention can be obtained by urea reaction or thiourea reaction using an isocyanate (R_1NCO) or isothiocyanate (R_1NCS) in an inert solvent with or without a base. The base includes an alkali metal carbonate (preferably sodium carbonate or potassium carbonate, etc.), an alkali metal hydrogencarbonate (preferably sodium hydrogencarbonate or potassium hydrogencarbonate, etc.), an alkali hydroxide (preferably sodium hydroxide or potassium hydroxide, etc.), a tertiary amine (preferably *N*,*N*-diisopropylethylamine, triethylamine, or

N-methylmorpholine, etc.), or an aromatic amine (preferably pyridine or imidazole, etc.). The inert solvent includes lower halocarbon solvents (preferably dichloromethane, dichloroethane, or chloroform, etc.), ethereal solvents (preferably tetrahydrofuran or dioxane), aromatic solvents (preferably benzene or toluene, etc.), or polar solvents (preferably *N*,*N*-dimethylformamide or dimethyl sulfoxide, etc.). Reaction temperature ranges from about -20 °C to 120 °C, preferably about 0 °C to 100 °C.

The novel urethane (A') of the present invention can be obtained by urethane reaction using R_1OCOX, wherein X is halogen such as chloro, bromo, or iodo, in an inert solvent with or without a base. The base includes an alkali metal carbonate (preferably sodium carbonate or potassium carbonate, etc.), an alkali metal hydrogencarbonate (preferably sodium hydrogencarbonate or potassium hydrogencarbonate, etc.), an alkali hydroxide (preferably sodium hydroxide or potassium hydroxide, etc.), a tertiary amine (preferably *N*,*N*-diisopropylethylamine, triethylamine, or *N*-methylmorpholine, etc.), or an aromatic amine (preferably pyridine, imidazole, or poly-(4-vinylpyridine), etc.). The inert solvent includes lower halocarbon solvents (preferably dichloromethane, dichloroethane, or chloroform, etc.), ethereal solvents (preferably tetrahydrofuran or dioxane), aromatic solvents (preferably benzene or toluene, etc.), or polar solvents (preferably *N*,*N*-dimethylformamide or dimethyl sulfoxide, etc.). Reaction temperature ranges from about -20 °C to 120 °C, preferably about 0 °C to 100 °C.

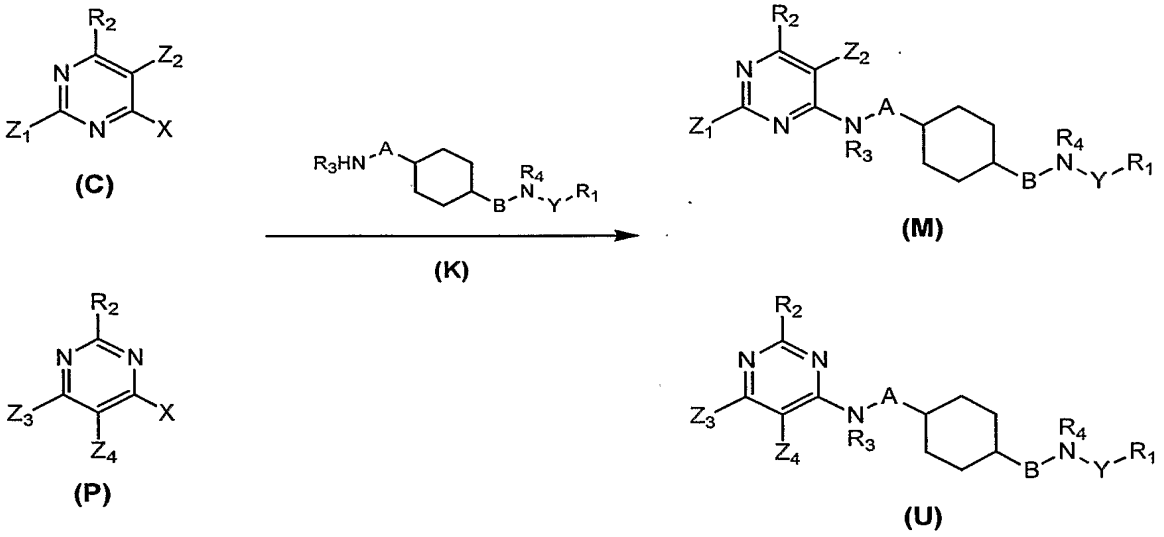
Scheme 6



Alternatively, the novel pyrimidines (M) and (U) of the present invention are directly synthesized from the pyrimidine core (C), which is synthesized in Scheme 1 and the pyrimidine core (P), which is synthesized in Scheme 5, as shown in Scheme 7. This coupling is performed with or without a base in an inert solvent. The base includes an alkali metal carbonate (preferably sodium carbonate or potassium carbonate, etc.), an alkali metal hydroxide (preferably sodium hydroxide, etc.), or a tertiary amine (preferably *N*,*N*-diisopropylethylamine, triethylamine, or *N*-methylmorpholine, etc.). The inert solvent

includes lower alkyl alcohol solvents (preferably methanol, ethanol, 2-propanol, or butanol, etc.) or amide solvents (preferably *N,N*-dimethylformamide or 1-methyl-pyrrolidin-2-one, etc.). Reaction temperature ranges from about 50 °C to 200 °C, preferably about 80 °C to 180 °C. Also this reaction can be carried out under microwave conditions.

Scheme 7



The common intermediate (C') of the novel amide (D') and the novel ester (E') in the present invention is prepared from condensation between the pyrimidine core (C) which is synthesized in Scheme 1 and the carboxylic acid (B'), wherein R_3, A, and B are as defined above, as shown in Scheme 8.

The carboxylic acid (C') is reacted with an amine (R_1NHR_4) and a dehydrating condensing agent in an inert solvent with or without a base to provide the novel amide (D') of the present invention. The dehydrating condensing agent includes dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC•HCl), bromo-tris-pyrrolidino-phosnium hexafluorophosphate (PyBroP), *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU), or 1-cyclohexyl-3-methylpolystyrene-carbodiimide. The base includes a tertiary amine (preferably *N,N*-diisopropylethylamine or triethylamine, etc.). The inert solvent includes lower halocarbon solvents (preferably dichloromethane, dichloroethane, or

chloroform, etc.), ethereal solvents (preferably tetrahydrofuran or dioxane), nitrile solvents (preferably acetonitrile, etc.), or amide solvents (preferably *N*,*N*-dimethylformamide, etc.). In case of need, 1-hydroxybenzotriazole (HOBT), HOBT-6-carboxaamidomethyl polystyrene, or 1-hydroxy-7-azabenzotriazole (HOAT) can be used as a reactant agent. Reaction temperature ranges from about -20 °C to 50 °C, preferably about 0 °C to 40 °C.

Alternatively, the novel amide (D') of the present invention can be obtained by amidation reaction via an acid chloride prepared from the carboxylic acid (C') and a base in an inert solvent. The base includes an alkali metal carbonate (preferably sodium carbonate or potassium carbonate, etc.), an alkali metal hydrogencarbonate (preferably sodium hydrogencarbonate or potassium hydrogencarbonate, etc.), an alkali hydroxide (preferably sodium hydroxide or potassium hydroxide, etc.), a tertiary amine (preferably *N*,*N*-diisopropylethylamine, triethylamine, or *N*-methylmorpholine, etc.), or an aromatic amine (preferably pyridine, imidazole, poly-(4-vinylpyridine), etc.). The inert solvent includes lower halocarbon solvents (preferably dichloromethane, dichloroethane, or chloroform, etc.), ethereal solvents (preferably tetrahydrofuran or dioxane), amide solvents (preferably *N*,*N*-dimethylformamide, etc.), or aromatic solvents (preferably toluene or pyridine, etc.). Reaction temperature ranges from about -20 °C to 50 °C, preferably about 0 °C to 40 °C.

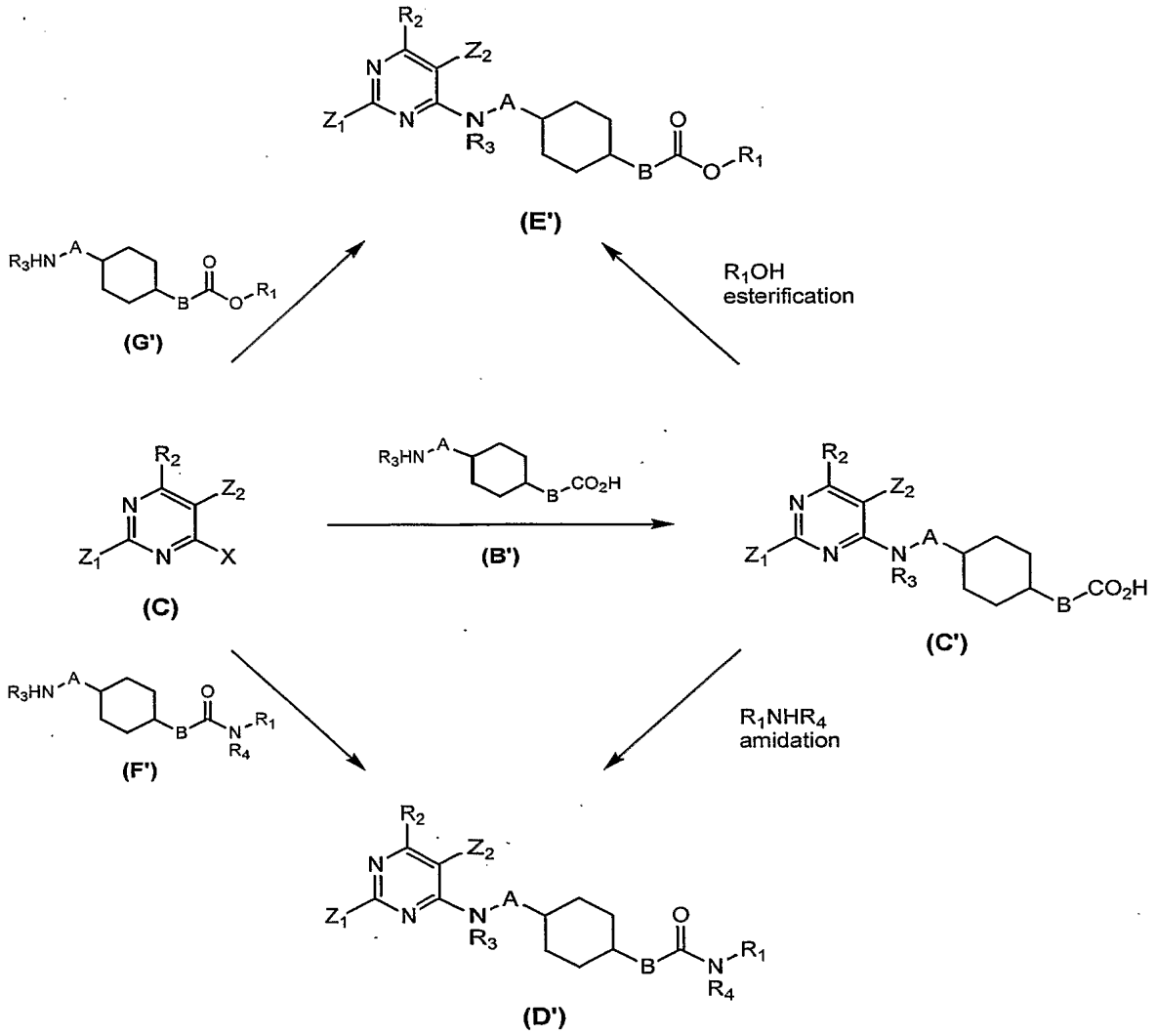
The carboxylic acid (C') is reacted with an alcohol (R_1OH) and a dehydrating condensing agent in an inert solvent with or without a base to provide the novel ester (E') of the present invention. The dehydrating condensing agent includes dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC•HCl), bromo-tris-pyrrolidino-phosnium hexafluorophosphate (PyBroP), *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU), or 1-cyclohexyl-3-methylpolystyrene-carbodiimide. The base includes a tertiary amine (preferably *N*,*N*-diisopropylethylamine or triethylamine, etc.). The inert solvent includes lower halocarbon solvents (preferably dichloromethane, dichloroethane, or chloroform, etc.), ethereal solvents (preferably tetrahydrofuran or dioxane), nitrile solvents

(preferably acetonitrile, etc.), or amide solvents (preferably *N*,*N*-dimethylformamide, etc.). In case of need, 1-hydroxybenzotriazole (HOBT), HOBT-6-carboxaamidomethyl polystyrene, or 1-hydroxy-7-azabenzotriazole (HOAT) can be used as a reactant agent. Reaction temperature ranges from about -20 °C to 50 °C, preferably about 0 °C to 40 °C.

Alternatively, the novel ester (E') of the present invention can be obtained by esterification via an acid chloride prepared from the carboxylic acid (C') and a base in an inert solvent. The base includes an alkali metal carbonate (preferably sodium carbonate or potassium carbonate, etc.), an alkali metal hydrogencarbonate (preferably sodium hydrogencarbonate or potassium hydrogencarbonate, etc.), an alkali hydroxide (preferably sodium hydroxide or potassium hydroxide, etc.), a tertiary amine (preferably *N*,*N*-diisopropylethylamine, triethylamine, or *N*-methylmorpholine, etc.), or an aromatic amine (preferably pyridine, imidazole, poly-(4-vinylpyridine), etc.). The inert solvent includes lower halocarbon solvents (preferably dichloromethane, dichloroethane, or chloroform, etc.), ethereal solvents (preferably tetrahydrofuran or dioxane), amide solvents (preferably *N*,*N*-dimethylformamide, etc.), or aromatic solvents (preferably toluene or pyridine, etc.). Reaction temperature ranges from about -20 °C to 50 °C, preferably about 0 °C to 40 °C.

Alternatively, the novel pyrimidines (D') and (E') of the present invention are directly synthesized from the pyrimidine core (C), which is synthesized in Scheme 1. This coupling is performed with or without a base in an inert solvent. The base includes an alkali metal carbonate (preferably sodium carbonate or potassium carbonate, etc.), an alkali metal hydroxide (preferably sodium hydroxide, etc.), or a tertiary amine (preferably *N*,*N*-diisopropylethylamine, triethylamine, or *N*-methylmorpholine, etc.). The inert solvent includes lower alkyl alcohol solvents (preferably methanol, ethanol, 2-propanol, or butanol, etc.) or amide solvents (preferably *N*,*N*-dimethylformamide or 1-methyl-pyrrolidin-2-one, etc.). Reaction temperature ranges from about 50 °C to 200 °C, preferably about 80 °C to 180 °C. Also this reaction can be carried out under microwave conditions.

Scheme 8



Examples

The compounds of the invention and their synthesis are further illustrated by the following examples. The following examples are provided to further define the invention without, however, limiting the invention to the particulas of these examples. "Ambient temperature" as referred to in the following example is meant to indicate a temperature falling between 0 °C and 40 °C. The following compounds are named by Beilstein Auto Nom Version 4.0, CS Chem Draw Ultra Version 7.0.1, CS Chem Draw Ultra Version 6.0.2, CS Chem Draw Ultra Version 6.0, or ACD Name Version 7.0.

Abbreviations used in the instant specification, particularly the Schemes and Examples, are as follows:

^{1}H NMR : proton nuclear magnetic resonance spectrum

AcOH : acetic acid

APCI : atmospheric pressure chemical ionization

$(Boc)_2O$: di-tertiary-butyl dicarbonate

BuLi : butyl lithium

BuOH : butanol

Cbz : carbobenzoxy

$CDCl_3$: deuterated chloroform

CH_2Cl_2 : dichloromethane

$CHCl_3$: chloroform

CI : chemical ionization

DCM : dichloromethane

DIEA : diisopropylethylamine

DMSO : dimethyl sulfoxide

EDC-HCl : 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

EI : electron ionization

ESI : electrospray ionization

Et_3N : triethylamine

Et_2O : diethyl ether

EtOAc : acetic acid ethyl ester

EtOH : ethanol

FAB : fast atom bombardment

HOBt-H_2O : 1-hydroxybenzotriazole hydrate

H_2SO_4 : sulfuric acid

HCl : hydrogen chloride

IPA : isopropanol

iPr_2NEt : diisopropylethylamine

K_2CO_3 : potassium carbonate

Me_2NH : dimethylamine

$MeNH_2$: methylamine

MeOH : methanol

$MgSO_4$: magnesium sulfate

$NaBH(OAc)_3$: sodium triacetoxyborohydride

$NaBH_3CN$: sodium cyanoborohydride

$NaBH_4$: sodium borohydride

NaH : sodium hydride

$NaHCO_3$: sodium hydrogencarbonate

NH_3 : ammonia

NH_4Cl : ammonium chloride

Pd/C : palladium carbon

$POCl_3$: phosphoryl chloride

$SOCl_2$: thionyl chloride

TFA : trifluoroacetic acid

THF : tetrahydrofuran

ZCl : benzyloxycarbonyl chloride

$ZnBr_2$: zinc bromide

s : singlet

d : doublet

t : triplet

q : qualtet

dd : doublet doublet

dt : doublet triplet

ddd : doublet doublet doublet

brs : broad singlet

m : multiplet

J : coupling constant

Hz : Hertz

Example 1

***N'*-(*cis*-4-{[4-Bromo-2-(trifluoromethoxy)benzyl]amino}cyclohexyl)-*N*,*N*-dimethylpyrimidine-4,6-diamine dihydrochloride**

Step A: Synthesis of (6-chloro-pyrimidin-4-yl)-dimethyl-amine.

To a solution of 4,6-dichloro-pyrimidine (10.0 g) in THF (10 mL) were added iPr_2NEt (10.4 g) and 50% aqueous Me_2NH (6.05 g). The mixture was stirred at ambient temperature for 28 hr and poured into saturated aqueous $NaHCO_3$. The aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was suspended in Et_2O. The precipitate was collected by filtration, washed with Et_2O and dried under reduced pressure to give (6-chloro-pyrimidin-4-yl)-dimethyl-amine (6.37 g).

ESI MS m/e 157, M^+; ^1H NMR (300 MHz, $CDCl_3$) δ 3.12 (s, 6 H), 6.41 (s, 1 H), 8.37 (s, 1 H).

Step B: Synthesis of *N*-(*cis*-4-bromo-2-trifluoromethoxy-benzyl)–cyclohexane-1,4-diamine.

To a solution of (4-amino-cyclohexyl)-carbamic acid tert-butyl ester (6.72 g) in $CHCl_3$ (67 mL) were added 4-bromo-2-trifluoromethoxy-benzaldehyde (8.44 g), acetic acid (1.88 g), and $NaBH(OAc)_3$ (9.97 g). The mixture was stirred at ambient temperature for 4 hr and poured into saturated aqueous $NaHCO_3$. The aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtrated, concentrated under reduced pressure, and purified by flash chromatography (silica gel, 33% EtOAc in hexane) to give [*cis*-4-(4-bromo-2-trifluoromethoxy-benzylamino)-cyclohexyl]-carbamic acid tert-butyl ester. To a solution of the above material (3.00 g) in

EtOAc (30 mL) was added 4 M hydrogen chloride in EtOAc (60 mL). The mixture was stirred at ambient temperature for 1 hr and concentrated under reduced pressure. The residue was alkalized with saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with $CHCl_3$ (seven times). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give *N*-(*cis*-4-bromo-2-trifluoromethoxy-benzyl)-cyclohexane-1,4-diamine (2.39 g).

ESI MS m/e 367, M^+; ^1H NMR (300 MHz, $CDCl_3$) δ 1.22-1.96 (m, 8 H), 2.51-2.71 (m, 1 H), 2.87-3.13 (m, 1 H), 3.74 (brs, 2 H), 7.28-7.50 (m, 3 H).

Step C: Synthesis of *N'*-(*cis*-4-{[4-bromo-2-(trifluoromethoxy)benzyl]amino}cyclohexyl)-*N*,*N*-dimethylpyrimidine-4,6-diamine dihydrochloride.

A mixture of *N*-(*cis*-4-bromo-2-trifluoromethoxy-benzyl)-cyclohexane-1,4-diamine (466 mg), (6-chloro-pyrimidin-4-yl)-dimethyl-amine (200 mg), and ethylene glycol (0.5 mL) was stirred at reflux for 4 hr in a sealed tube. The mixture was poured into saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtered, concentrated under reduced pressure, and purified by flash chromatography (NH-silica gel, 50% EtOAc in hexane and silica gel, 5% MeOH in $CHCl_3$) to give *N'*-(*cis*-4-{[4-bromo-2-(trifluoromethoxy)benzyl]amino}cyclohexyl)-*N*,*N*-dimethylpyrimidine-4,6-diamine. To a solution of the above material in EtOAc (2 mL) was added 4 M hydrogen chloride in EtOAc (10 mL). The mixture was stirred at ambient temperature for 1 hr and concentrated under reduced pressure. The residue was suspended in Et_2O (20 mL) and the suspension was stirred at ambient temperature for 4 hr. The precipitate was collected by filtration, washed with Et_2O, and dried under reduced pressure to give *N'*-(*cis*-4-{[4-bromo-2-(trifluoromethoxy)benzyl]amino}cyclohexyl)-*N*,*N*-dimethylpyrimidine-4,6-diamine dihydrochloride (67 mg).

ESI MS m/e 488, M (free) + H^+; ^1H NMR (300 MHz, $CDCl_3$) δ 1.64-1.86 (m, 2 H), 1.96-2.34 (m, 8 H), 2.98-3.44 (m, 8 H), 4.27 (s, 2 H), 7.40-7.59 (m, 3 H), 8.06-8.24 (m, 2 H).

Example 2

***N*-(*cis*-4-{[6-(Dimethylamino)pyrimidin-4-yl]amino}cyclohexyl)-3,4-difluorobenzamide hydrochloride**

Step A: Synthesis of (*cis*-4-{[1-(3,4-difluoro-phenyl)-methanoyl]-amino}-cyclohexyl)-carbamic acid *tert*-butyl ester.

To a solution of 3,4-difluoro-benzoic acid (4.10 g) and (*cis*-4-amino-cyclohexyl)-carbamic acid *tert*-butyl ester (5.05 g) in DMF (50 mL) were added Et_3N (90 mL), HOBt-H_2O (5.41 g), and EDC-HCl (4.97 g). The mixture was stirred at ambient temperature for 17 hr. To the reaction mixture was added water (200 mL) and the suspension was stirred at ambient temperature for 10 min. The precipitate was collected by filtration, washed with H_2O and EtOH, and dried at 80 °C under reduced pressure to give (*cis*-4-{[1-(3,4-difluoro-phenyl)-methanoyl]-amino}-cyclohexyl)-carbamic acid *tert*-butyl ester (5.20 g). ESI MS m/e 377, $M + Na^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9 H), 1.53-1.95 (m, 8 H), 3.60-3.74 (m, 1 H), 4.00-4.16 (m, 1 H), 4.50-4.68 (m, 1 H), 5.95-6.09 (m, 1 H), 7.15-7.28 (m, 1 H), 7.43-7.68 (m, 2 H).

Step B: Synthesis of *N*-(*cis*-4-amino-cyclohexyl)-3,4-difluoro-benzamide.

A solution of (*cis*-4-{[1-(3,4-difluoro-phenyl)-methanoyl]-amino}-cyclohexyl)-carbamic acid *tert*-butyl ester (5.20 g) in EtOAc (52 mL) was cooled on an ice-bath and 4 M hydrogen chloride in EtOAc (104 mL) was added. The mixture was stirred at ambient temperature for 1 hr and concentrated under reduced pressure. The residue was dissolved in 1 M aqueous NaOH and the aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtered, concentrated under reduced pressure, and dried at 60 °C under reduced pressure to give *N*-(*cis*-4-amino-cyclohexyl)-3,4-difluoro-benzamide (3.00 g).

ESI MS m/e 255, $M + H^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 1.15-1.52 (m, 3 H), 1.59-1.89 (m, 5 H), 2.94-3.06 (m, 1 H), 4.06-4.20 (m, 1 H), 6.01-6.18 (m, 1 H), 7.13-7.26 (m, 1 H), 7.43-7.50 (m, 1 H), 7.57-7.67 (m, 1 H).

Step C: Synthesis of *N*-(*cis*-4-{[6-(dimethylamino)pyrimidin-4-yl]amino}cyclohexyl)-3,4-difluorobenzamide hydrochloride.

To a solution of *N*-(*cis*-4-amino-cyclohexyl)-3,4-difluoro-benzamide (442 mg) was added (6-chloro-pyrimidin-4-yl)-dimethyl-amine obtained in step A of example 1 (250 mg). The mixture was stirred at 180°C for 8 hr in a sealed tube. To the mixture was added saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtered, concentrated under reduced pressure, and purified by flash chromatography (NH-silica gel, 33% to 50% EtOAc in hexane and silica gel, 3% MeOH in $CHCl_3$) to give *N*-(*cis*-4-{[6-(dimethylamino)pyrimidin-4-yl]amino}cyclohexyl)-3,4-difluorobenzamide. To a solution of the above material in EtOAc (10 mL) was added 4 M hydrogen chloride in EtOAc (0.2 mL). The mixture was stirred at ambient temperature for 1 hr and concentrated under reduced pressure. The residue was suspended in Et_2O (20 mL) and the suspension was stirred at ambient temperature for 4 hr. The precipitate was collected by filtration, washed with Et_2O, and dried at 70°C under reduced pressure to give *N*-(*cis*-4-{[6-(dimethylamino)pyrimidin-4-yl]amino}cyclohexyl)-3,4-difluorobenzamide hydrochloride (99 mg).

ESI MS m/e 398, M (free) + Na^+; ^1H NMR (300 MHz, $CDCl_3$) δ 1.69-2.15 (m, 8 H), 3.00-3.42 (m, 6 H), 3.69-3.81 (m, 1 H), 4.03-4.21 (m, 1 H), 5.26 (s, 1 H), 6.66-6.80 (m, 1 H), 7.13-7.26 (m, 1 H), 7.51-7.62 (m, 1 H), 7.68-7.80 (m, 1 H), 8.01 (s, 1 H), 8.68-8.91 (m, 1 H), 13.84-14.09 (m, 1 H).

Example 3

***N*-[*cis*-4-({[6-(Dimethylamino)pyrimidin-4-yl]amino}methyl)cyclohexyl]-3,4-difluorobenzamide hydrochloride**

Step A: Synthesis of (*cis*-4-hydroxymethyl-cyclohexyl)-carbamic acid *tert*-butyl ester.

A suspension of *cis*-4-amino-cyclohexanecarboxylic acid (244 g) in MeOH (2.45 L) was cooled to -8 °C. Thionyl chloride (45.0 mL) was added dropwise. The mixture was

stirred at ambient temperature for 4.5 hr and concentrated under reduced pressure to give a white solid. To a suspension of the above solid in $CHCl_3$ (3.00 L) were added triethylamine (261 mL) and $(Boc)_2O$ (409 g) successively. The mixture was stirred at ambient temperature for 5 hr and poured into water. The aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtrated, concentrated under reduced pressure, and purified by flash chromatography (silica gel, $CHCl_3$ to 10% MeOH in $CHCl_3$) to give a colorless oil (531 g). To a suspension cooled at -4 °C of lithium aluminum hydride (78.3 g) in Et_2O (7.9 L) was added a solution of the above oil (530.9 g) in Et_2O (5.3 L) below 0 °C. The resulting suspension was stirred at ambient temperature for 2 hr. The mixture was cooled on an ice-bath, quenched with cold water, and filtrated through a pad of celite. The filtrate was dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. The precipitate was suspended in hexane (300 mL), filtrated, washed with hexane, and dried under reduced pressure to give (*cis*-4-hydroxymethyl-cyclohexyl)-carbamic acid *tert*-butyl ester (301 g).

ESI MS m/e 252, $M + Na^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 1.16-1.36 (m, 2 H), 1.45 (s, 9 H), 1.52-1.77 (m, 7 H), 3.51 (d, J = 6.2 Hz, 2 H), 3.75 (brs, 1 H), 4.30-4.82 (m, 1 H).

Step B: Synthesis of [*cis*-4-(benzyloxycarbonylamino-methyl)-cyclohexyl]-carbamic acid *tert*-butyl ester.

To a solution of (*cis*-4-hydroxymethyl-cyclohexyl)-carbamic acid *tert*-butyl ester (17.7 g) in THF (245 mL) were added triphenylphosphine (20.2 g) and phthalimide (11.4 g) successively. The resulting suspension was cooled on an ice-bath and 40% diethyl azodicarboxylate in toluene (33.6 mL) was added over 1 hr. The mixture was stirred at ambient temperature for 2.5 days, concentrated under reduced pressure, and purified by flash chromatography (silica gel, 33% EtOAc in hexane) to give a white solid. To a suspension of the above solid (27.5 g) in EtOH (275 mL) was added hydrazine hydrate (5.76 g). The mixture was stirred at reflux for 2.25 hr, cooled to ambient temperature, and concentrated under reduced pressure. The precipitate was dissolved in 10% aqueous sodium hydroxide (350 mL). The aqueous layer was extracted with $CHCl_3$ (three times).

The combined organic layer was dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. To a solution of the above residue in $CHCl_3$ (275 mL) was added triethylamine (8.54 g). The resulting solution was cooled to 0 °C and ZCl (14.4 g) was added below 5 °C. The mixture was stirred at ambient temperature for 16 hr and poured into saturated aqueous $NaHCO_3$. The aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtrated, concentrated under reduced pressure, and purified by flash chromatography (silica gel, 2% MeOH in $CHCl_3$) to give [*cis*-4-(benzyloxycarbonylamino-methyl)-cyclohexyl]-carbamic acid *tert*-butyl ester (25.3 g).

ESI MS m/e 385, $M + Na^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 1.13-1.31 (m, 2 H), 1.44 (s, 9 H), 1.48-1.75 (m, 7 H), 3.10 (t, J = 6.4 Hz, 2 H), 3.72 (brs, 1 H), 4.42-4.76 (m, 1 H), 4.76-4.92 (m, 1 H), 5.09 (s, 2 H), 7.27-7.38 (m, 5 H).

Step C: Synthesis of (*cis*-4-amino-cyclohexylmethyl)-carbamic acid benzyl ester.

To a solution of [*cis*-4-(benzyloxycarbonylamino-methyl)-cyclohexyl]-carbamic acid *tert*-butyl ester (12.9 g) in EtOAc (129 mL) was added 4 M hydrogen chloride in EtOAc (129 mL). The mixture was stirred at ambient temperature for 3 hr, filtrated, washed with EtOAc, and dried under reduced pressure. To the residue was added saturated aqueous $NaHCO_3$. The aqueous layer was extracted with $CHCl_3$ (five times). The combined organic layer was dried over $MgSO_4$, filtrated, concentrated under reduced pressure, and dried under reduced pressure to give (*cis*-4-amino-cyclohexylmethyl)-carbamic acid benzyl ester (8.88 g).

ESI MS m/e 263, $M + H^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 1.36-1.98 (m, 9 H), 2.96-3.32 (m, 3 H), 5.12 (brs, 3 H), 7.36 (s, 5 H).

Step D: Synthesis of [*cis*-4-(3,4-difluoro-benzoylamino)-cyclohexylmethyl]-carbamic acid benzyl ester.

To a solution of (*cis*-4-amino-cyclohexylmethyl)-carbamic acid benzyl ester (2.00 g) in $CHCl_3$ (16 mL) were added Et_3N (2.23 mL) and 3,4-difluoro-benzoyl chloride (1.48 g) in $CHCl_3$ (4 mL). The mixture was stirred at ambient temperature for 12 hr and poured

into saturated aqueous $NaHCO_3$. The aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtered, concentrated under reduced pressure, and purified by medium-pressure liquid chromatography (NH-silica gel, 20% to 50% EtOAc in hexane) to give [*cis*-4-(3,4-difluoro-benzoylamino)-cyclohexylmethyl]-carbamic acid benzyl ester (2.66 g).

ESI MS m/e 425, M^+; ^1H NMR (300 MHz, $CDCl_3$) δ 1.22-1.44 (m, 2 H), 1.57-1.88 (m, 6 H), 3.07-3.25 (m, 2 H), 4.08-4.28 (m, 1 H), 4.78-4.93 (m, 1 H), 5.10 (s, 2 H), 6.02-6.24 (m, 1 H), 7.13-7.39 (m, 6 H), 7.43-7.52 (m, 1 H), 7.58-7.68 (m, 1 H).

Step E: Synthesis of *N*-(*cis*-4-aminomethyl-cyclohexyl)-3,4-difluoro-benzamide.

To a solution of [*cis*-4-(3,4-difluoro-benzoylamino)-cyclohexylmethyl]-carbamic acid benzyl ester (2.60 g) in MeOH (26 mL) was added 10% Pd/C (260 mg). The mixture was stirred at ambient temperature under hydrogen atmosphere for 84 hr. The mixture was filtrated through a pad of celite, concentrated under reduced pressure, and purified by medium-pressure liquid chromatography (NH-silica gel, 9% to 17% EtOAc in hexane and silica gel, 1% MeOH in $CHCl_3$) to give *N*-(*cis*-4-aminomethyl-cyclohexyl)-3,4-difluoro-benzamide (1.43 g).

ESI MS m/e 269, $M + H^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 1.13-1.86 (m, 9 H), 2.64 (d, J = 6.5 Hz, 2 H), 4.16-4.28 (m, 1 H), 6.09-6.30 (m, 1 H), 7.15-7.27 (m, 1 H), 7.46-7.53 (m, 1 H), 7.58-7.67 (m, 1 H).

Step F: Synthesis of *N*-[*cis*-4-({[6-(dimethylamino)pyrimidin-4-yl]amino}methyl)cyclohexyl]-3,4-difluorobenzamide hydrochloride.

To a solution of *N*-(*cis*-4-aminomethyl-cyclohexyl)-3,4-difluoro-benzamide (373 mg) in BuOH (1 mL) was added (6-chloro-pyrimidin-4-yl)-dimethyl-amine obtained in step A of example 1 (200 mg). The mixture was heated in a microwave synthesizer at 220°C for 20 min. To the mixture was added saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtrated, concentrated under reduced pressure, and purified by medium-pressure liquid chromatography (NH-silica gel, 20% to 50% EtOAc in hexane) to give *N*-[*cis*-4-

({[6-(dimethylamino)pyrimidin-4-yl]amino}methyl)cyclohexyl]-3,4-difluorobenzamide. To a solution of the above material in EtOAc (10 mL) was added 4 M hydrogen chloride in EtOAc (0.5 mL). The mixture was stirred at ambient temperature for 30 min and concentrated under reduced pressure. A suspension of the above material in Et_2O (12 mL) was stirred at ambient temperature for 2 hr. The precipitate was collected by filtration, washed with Et_2O, and dried at 70°C under reduced pressure to give *N*-[*cis*-4-({[6-(dimethylamino)pyrimidin-4-yl]amino}-methyl)cyclohexyl]-3,4-difluorobenzamide hydrochloride (106 mg).

ESI MS m/e 390, M (free) + H^+; ^1H NMR (300 MHz, $CDCl_3$) δ 1.31-2.14 (m, 8 H), 2.96-3.46 (m, 8 H), 4.40-4.61 (m, 1 H), 5.18 (s, 1 H), 7.14-7.35 (m, 2 H), 7.83-8.09 (m, 3 H), 8.79-9.14 (m, 1 H).

Example 4

***N*-[(*cis*-4-{[6-(Dimethylamino)pyrimidin-4-yl]amino}cyclohexyl)methyl]-3,4-difluorobenzamide hydrochloride**

Step A: Synthesis of {*cis*-4-[(3,4-difluoro-benzoylamino)-methyl]-cyclohexyl}-carbamic acid tert-butyl ester.

To a solution of [*cis*-4-(benzyloxycarbonylamino-methyl)-cyclohexyl]-carbamic acid *tert*-butyl ester obtained in step B of example 3 (5.00 g) in MeOH (50 mL) was added 10% Pd/C (500 mg). The mixture was stirred at ambient temperature under hydrogen atmosphere for 84 hr, filtrated through a pad of celite, and concentrated under reduced pressure to give a pale brown oil. To a solution of the above oil in $CHCl_3$ (40 mL) were added Et_3N (4.03 mL) and 3,4-difluoro-benzoyl chloride (2.68 g) in $CHCl_3$ (10 mL). The mixture was stirred at ambient temperature for 12 hr. To the mixture was added saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtered, concentrated under reduced pressure, and purified by medium-pressure liquid chromatography (NH-silica gel, 50% EtOAc in hexane) to give {*cis*-4-[(3,4-difluoro-benzoylamino)-methyl]-cyclohexyl}-

carbamic acid tert-butyl ester (3.48 g).

ESI MS m/e 391, M + Na^+; ^1H NMR (300 MHz, $CDCl_3$) δ 1.19-1.81 (m, 16 H), 3.33-3.43 (m, 2 H), 3.68-3.79 (m, 1 H), 4.54-4.73 (m, 1 H), 6.10-6.21 (m, 1 H), 7.17-7.27 (m, 1 H), 7.46-7.54 (m, 1 H), 7.59-7.68 (m, 1 H).

Step B: Synthesis of *N*-(*cis*-4-amino-cyclohexylmethyl)-3,4-difluoro-benzamide.

To a solution of {*cis*-4-[(3,4-difluoro-benzoylamino)-methyl]-cyclohexyl}-carbamic acid tert-butyl ester (3.48 g) in EtOAc (35 mL) was added 4 M hydrogen chloride in EtOAc (35 mL). The mixture was stirred at ambient temperature for 12 hr and concentrated under reduced pressure. The residue was dissolved in 1 M aqueous NaOH and the aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtrated, concentrated under reduced pressure to give *N*-(*cis*-4-amino-cyclohexylmethyl)-3,4-difluoro-benzamide (2.50 g).

ESI MS m/e 269, M + H^+; ^1H NMR (300 MHz, $CDCl_3$) δ 1.16-1.81 (m, 9 H), 2.93-3.08 (m, 1 H), 3.32-3.42 (m, 2 H), 6.41-6.57 (m, 1 H), 7.14-7.27 (m, 1 H), 7.48-7.57 (m, 1 H), 7.60-7.71 (m, 1 H).

Step C: Synthesis of *N*-[(*cis*-4-{[6-(dimethylamino)pyrimidin-4-yl]amino}cyclohexyl)methyl]-3,4-difluorobenzamide hydrochloride.

To a solution of *N*-(*cis*-4-amino-cyclohexylmethyl)-3,4-difluoro-benzamide (469 mg) in BuOH (1 mL) was added (6-chloro-pyrimidin-4-yl)-dimethyl-amine obtained in step A of example 1 (250 mg). The mixture was heated in a microwave synthesizer at 220°C for 20 min. To the mixture was added saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtrated, concentrated under reduced pressure, and purified by medium-pressure liquid chromatography (NH-silica gel, 20% to 50% EtOAc in hexane) to give *N*-[(*cis*-4-{[6-(dimethylamino)pyrimidin-4-yl]amino}cyclohexyl)methyl]-3,4-difluorobenzamide.

To a solution of the above material in EtOAc (10 mL) was added 4 M hydrogen chloride in EtOAc (0.5 mL). The mixture was stirred at ambient temperature for 30 min and concentrated under reduced pressure. A suspension of the residue in Et_2O (12 mL) was

stirred at ambient temperature for 2 hr. The precipitate was collected by filtration, washed with Et_2O, and dried at 70°C under reduced pressure to give *N*-[(*cis*-4-{[6-(dimethylamino)pyrimidin-4-yl]amino}-cyclohexyl)methyl]-3,4-difluorobenzamide hydrochloride (82 mg).

ESI MS m/e 390, M (free) + H^+; ^1H NMR (300 MHz, $CDCl_3$) δ 1.50-2.04 (m, 9 H), 2.93-3.57 (m, 8 H), 3.67-3.85 (m, 1 H), 5.23 (s, 1 H), 6.85-7.35 (m, 2 H), 7.73-8.05 (m, 3 H), 8.75-9.01 (m, 1 H), 13.64-13.95 (m, 1 H).

Example 5

***N*-(*cis*-4-{[6-(Dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-3,4-difluorobenzamide hydrochloride**

Step A: Synthesis of 4,6-dichloro-2-methyl-pyrimidine.

A suspension of 2-methyl-pyrimidine-4,6-diol (20.0 g) in $POCl_3$ (162 mL) was stirred at reflux for 4 hr and cooled to ambient temperature. The mixture was poured into ice water (3 L). The aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtrated, and concentrated under reduced pressure to give 4,6-dichloro-2-methyl-pyrimidine (22.37 g).

CI MS m/e 163, M^+; ^1H NMR (300 MHz, $CDCl_3$) δ 2.71 (s, 3 H), 7.25 (s, 1 H).

Step B: Synthesis of (6-chloro-2-methyl-pyrimidin-4-yl)-dimethyl-amine.

To a solution of 4,6-dichloro-2-methyl-pyrimidine (11.1 g) in THF (110 mL) were added iPr_2NEt (14.2 mL) and 50% aqueous Me_2NH (8.5 mL). The mixture was stirred at ambient temperature for 2 hr. To the mixture was added 50% aqueous Me_2NH (3.5 mL) and stirred at ambient temperature for 7 hr and concentrated under reduced pressure. To the residue was added saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtered, concentrated under reduced pressure, and dried under reduced pressure to give (6-chloro-2-methyl-pyrimidin-4-yl)-dimethyl-amine (11.6 g).

ESI MS m/e 172, M + H^+; ^1H NMR (300 MHz, $CDCl_3$) δ 2.49 (s, 3 H), 3.10 (s, 6 H), 6.24

(s, 1 H).

Step C: Synthesis of *N*-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-3,4-difluorobenzamide hydrochloride.

To a solution of *N*-(*cis*-4-amino-cyclohexyl)-3,4-difluoro-benzamide obtained in step B of example 2 (407 mg) in BuOH (1 mL) was added (6-chloro-2-methyl-pyrimidin-4-yl)-dimethyl-amine (250 mg). The mixture was heated in a microwave synthesizer at 200°C for 20 min and 230°C for 20 min. To the mixture was added saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtrated, concentrated under reduced pressure, and purified by medium-pressure liquid chromatography (NH-silica gel, 20% to 50% EtOAc in hexane) to give *N*-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}-cyclohexyl)-3,4-difluorobenzamide. To a solution of the above material in EtOAc (10 mL) was added 4 M hydrogen chloride in EtOAc (0.2 mL). The mixture was stirred at ambient temperature for 1 hr and concentrated under reduced pressure. A suspension of the residue in Et_2O (12 mL) was stirred at ambient temperature for 2 hr. The precipitate was collected by filtration, washed with Et_2O, and dried at 70°C under reduced pressure to give *N*-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-3,4-difluorobenzamide hydrochloride (325 mg).

ESI MS m/e 412, M (free) + Na^+; ^1H NMR (300 MHz, $CDCl_3$) δ 1.63-2.03 (m, 8 H), 2.49 (s, 3 H), 2.91-3.43 (m, 6 H), 3.67-3.79 (m, 1 H), 4.03-4.22 (m, 1 H), 5.15 (s, 1 H), 6.89-7.02 (m, 1 H), 7.14-7.27 (m, 1 H), 7.56-7.64 (m, 1 H), 7.69-7.81 (m, 1 H), 8.40-8.55 (m, 1 H).

Example 6

3-Chloro-*N*-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-4-fluorobenzamide hydrochloride

Step A: Synthesis of *cis*-*N*-benzyl-cyclohexane-1,4-diamine.

To a solution of (*cis*-4-amino-cyclohexyl)-carbamic acid tert-butyl ester (5.00 g) in

$CHCl_3$ (100 mL) were added benzaldehyde (2.48 g) and acetic acid (1.40 g). The mixture was stirred at ambient temperature for 1 hr. To the mixture was added $NaBH(OAc)_3$ (7.42 g) and the mixture was stirred at ambient temperature for 15 hr. The reaction was quenched with saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtrated, concentrated under reduced pressure, and purified by medium-pressure liquid chromatography (silica gel, 2% to 9% MeOH in $CHCl_3$) to give (*cis*-4-benzylamino-cyclohexyl)-carbamic acid tert-butyl ester (76.9 g). To a solution of the above material (76.9 g) in EtOAc (77 mL) was added 4 M hydrogen chloride in EtOAc (38.5 mL). The mixture was stirred at ambient temperature for 10 hr and concentrated under reduced pressure. The residue was dissolved in 2M aqueous NaOH (150 mL) and the aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtered, concentrated under reduced pressure, and dried under reduced pressure to give *cis*-*N*-benzyl-cyclohexane-1,4-diamine (4.12 g).

ESI MS m/e 205, $M + H^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 1.42-1.72 (m, 8 H), 2.63-2.74 (m, 1 H), 2.80-2.91 (m, 1 H), 3.77 (s, 2 H), 7.20-7.39 (m, 5 H).

Step B: Synthesis of *N*-(*cis*-4-benzylamino-cyclohexyl)-2,*N'*,*N'*-trimethyl-pyrimidine-4,6-diamine.

To a solution of (6-chloro-2-methyl-pyrimidin-4-yl)-dimethyl-amine obtained in step B of example 5 (763 mg) in BuOH (0.8 mL) was added *cis*-*N*-benzyl-cyclohexane-1,4-diamine (1.00 g). The mixture was heated in a microwave synthesizer at 220°C for 25 min. To the mixture was added saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtrated, concentrated under reduced pressure, and purified by medium-pressure liquid chromatography (NH-silica gel, 9% to 60% EtOAc in hexane) to give *N*-(*cis*-4-benzylamino-cyclohexyl)-2,*N'*,*N'*-trimethyl-pyrimidine-4,6-diamine (952 mg).

ESI MS m/e 340, $M + H^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 1.47-1.92 (m, 8 H), 2.35 (s, 3 H), 2.63-2.74 (m, 1 H), 3.04 (s, 6 H), 3.56-3.69 (m, 1 H), 3.79 (s, 2 H), 4.67-4.80 (m, 1 H),

5.14 (s, 1 H), 7.20-7.36 (m, 5 H).

Step C: Synthesis of *N*-(*cis*-4-amino-cyclohexyl)-2,*N'*,*N'*-trimethyl-pyrimidine-4,6-diamine.

To a solution of *N*-(*cis*-4-benzylamino-cyclohexyl)-2,*N'*,*N'*-trimethyl-pyrimidine-4,6-diamine (940 mg) in MeOH (9.4 mL) was added 20% $Pd(OH)_2$ (188 mg). The mixture was stirred at 50°C under hydrogen atmosphere for 10 hr. The mixture was filtrated through a pad of celite, concentrated under reduced pressure, and purified by medium-pressure liquid chromatography (NH-silica gel, 2% to 5% MeOH in $CHCl_3$) to give *N*-(*cis*-4-amino-cyclohexyl)-2,*N'*,*N'*-trimethyl-pyrimidine-4,6-diamine (566 mg).

ESI MS m/e 250, $M + H^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 1.05-1.89 (m, 10 H), 2.35 (s, 3 H), 2.75-2.90 (m, 1 H), 3.05 (s, 6 H), 3.54-3.70 (m, 1 H), 4.68-4.82 (m, 1 H), 5.14 (s, 1 H).

Step D: Synthesis of 3-chloro-*N*-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}-cyclohexyl)-4-fluorobenzamide hydrochloride.

To a solution of 3-chloro-4-fluoro-benzoic acid (192 mg) and *N*-(*cis*-4-amino-cyclohexyl)-2,*N'*,*N'*-trimethyl-pyrimidine-4,6-diamine (250 mg) in DMF (4 mL) were added Et_3N (0.34 mL), HOBt-H_2O (230 mg), and EDC-HCl (211 mg). The mixture was stirred at ambient temperature for 12 hr. To the mixture was added water (20 mL) and the aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtrated, concentrated under reduced pressure, and purified by medium-pressure liquid chromatography (NH-silica gel, 25% to 50% EtOAc in hexane) to give 3-chloro-*N*-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}-cyclohexyl)-4-fluorobenzamide. To a solution of the above material in EtOAc (10 mL) was added 4 M hydrogen chloride in EtOAc (0.2 mL). The mixture was stirred at ambient temperature for 1 hr and concentrated. The residue was suspended in Et_2O (20 mL) and the suspension was stirred at ambient temperature for 2 hr. The precipitate was collected by filtration, washed with Et_2O, and dried at 70°C under reduced pressure to give 3-chloro-*N*-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}-cyclohexyl)-4-fluorobenzamide hydrochloride (196 mg).

ESI MS m/e 406, M (free) + H^+; ^1H NMR (300 MHz, $CDCl_3$) δ 1.62-2.00 (m, 8 H), 2.49 (s, 3 H), 2.99-3.40 (m, 6 H), 3.67-3.79 (m, 1 H), 4.02-4.20 (m, 1 H), 5.15 (s, 1 H), 6.59-6.70 (m, 1 H), 7.11-7.26 (m, 1 H), 7.67-7.79 (m, 1 H), 7.89-8.02 (m, 1 H), 8.48-8.61 (m, 1 H).

Example 7

***N*-(*cis*-4-{[6-(Dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-4-fluorobenzamide hydrochloride**

To a solution of *N*-(*cis*-4-amino-cyclohexyl)-2,*N'*,*N'*-trimethyl-pyrimidine-4,6-diamine obtained in step C of example 6 (250 mg) in $CHCl_3$ (3 mL) were added Et_3N (0.29 mL) and 4-fluoro-benzoyl chloride (174 mg). The mixture was stirred at ambient temperature for 12 hr. The reaction was quenched with saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtered, concentrated under reduced pressure, and purified by medium-pressure liquid chromatography (NH-silica gel, 25% to 50% EtOAc in hexane) to give *N*-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}-cyclohexyl)-4-fluorobenzamide. To a solution of the above material in EtOAc (10 mL) was added 4 M hydrogen chloride in EtOAc (0.2 mL). The mixture was stirred at ambient temperature for 1 hr and concentrated under reduced pressure. The residue was suspended in Et_2O (20 mL) and the suspension was stirred at ambient temperature for 2 hr. The precipitate was collected by filtration, washed with Et_2O, and dried at 70°C under reduced pressure to give *N*-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-4-fluorobenzamide hydrochloride (255 mg).

ESI MS m/e 372, M (free) + H^+; ^1H NMR (300 MHz, $CDCl_3$) δ 1.66-2.03 (m, 8 H), 2.49 (s, 3 H), 2.93-3.43 (m, 6 H), 3.64-3.78 (m, 1 H), 4.04-4.20 (m, 1 H), 5.14 (s, 1 H), 6.43-6.56 (m, 1 H), 7.05-7.15 (m, 2 H), 7.75-7.91 (m, 2 H), 8.47-8.63 (m, 1 H).

Example 8

3,4-Dichloro-*N*-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-

yl]amino}cyclohexyl)-benzamide hydrochloride

Using the procedure for the step A of example 7, the title compound was obtained. ESI MS m/e 422, M (free)$^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.63-2.02 (m, 8 H), 2.49 (s, 3 H), 2.96-3.38 (m, 6 H), 3.67-3.80 (m, 1 H), 4.02-4.21 (m, 1 H), 5.14 (s, 1 H), 6.69-6.80 (m, 1 H), 7.47-7.53 (m, 1 H), 7.62-7.70 (m, 1 H), 7.93-8.00 (m, 1 H), 8.48-8.59 (m, 1 H), 13.70-13.90 (m, 1 H).

Example 9

4-Chloro-*N*-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-3-fluorobenzamide hydrochloride

Using the procedure for the step D of example 6, the title compound was obtained. ESI MS m/e 406, M (free) + H$^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.66-2.07 (m, 8 H), 2.48 (s, 3 H), 2.94-3.40 (m, 6 H), 3.66-3.79 (m, 1 H), 4.00-4.21 (m, 1 H), 5.14 (s, 1 H), 6.88-7.00 (m, 1 H), 7.40-7.48 (m, 1 H), 7.52-7.60 (m, 1 H), 7.65-7.73 (m, 1 H), 8.45-8.54 (m, 1 H), 13.66-13.86 (m, 1 H).

Example 10

3-Chloro-*N*-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-5-fluorobenzamide hydrochloride

Using the procedure for the step D of example 6, the title compound was obtained. ESI MS m/e 406, M (free) + H$^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.61-2.07 (m, 8 H), 2.49 (s, 3 H), 2.96-3.41 (m, 6 H), 3.65-3.79 (m, 1 H), 4.00-4.22 (m, 1 H), 5.14 (s, 1 H), 6.78-6.88 (m, 1 H), 7.16-7.23 (m, 1 H), 7.42-7.50 (m, 1 H), 7.60-7.64 (m, 1 H), 8.36-8.62 (m, 1 H), 13.75-13.95 (m, 1 H).

Example 11

***N*-(*cis*-4-{[6-(Dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-3,4,5-trifluorobenzamide hydrochloride**

Using the procedure for the step D of example 6, the title compound was obtained. ESI MS m/e 408, M (free) + H^+; ^1H NMR (300 MHz, $CDCl_3$) δ 1.64-2.04 (m, 8 H), 2.48 (s, 3 H), 2.92-3.42 (m, 6 H), 3.65-3.79 (m, 1 H), 4.00-4.20 (m, 1 H), 5.15 (s, 1 H), 6.73-6.84 (m, 1 H), 7.48-7.58 (m, 2 H), 8.47-8.60 (m, 1 H), 13.70-13.86 (m, 1 H).

Example 12

5-Bromo-*N*-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-nicotinamide dihydrochloride

Using the procedure for the step D of example 6, the title compound was obtained. ESI MS m/e 433, M (free)$^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 1.67-2.18 (m, 8 H), 2.49 (s, 3 H), 2.91-3.45 (m, 6 H), 3.60-3.80 (m, 1 H), 4.10-4.28 (m, 1 H), 5.11-5.20 (m, 1 H), 7.70-7.87 (m, 1 H), 8.33-8.49 (m, 1 H), 8.60-8.67 (m, 1 H), 8.90-9.02 (m, 1 H), 9.17-9.30 (m, 1 H).

Example 13

***N*-(*cis*-4-{[6-(Dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-3,5-difluorobenzamide hydrochloride**

Using the procedure for the step A of example 7, the title compound was obtained. ESI MS m/e 390, M (free) + H^+; ^1H NMR (300 MHz, $CDCl_3$) δ 1.63-2.03 (m, 8 H), 2.48 (s, 3 H), 2.99-3.45 (m, 6 H), 3.69-3.79 (m, 1 H), 4.03-4.19 (m, 1 H), 5.14 (s, 1 H), 6.58-6.71 (m, 1 H), 6.86-6.98 (m, 1 H), 7.28-7.44 (m, 2 H), 8.50-8.64 (m, 1 H), 13.75-13.93 (m, 1 H).

Example 14

***N*-(*cis*-4-{[6-(Dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-4-fluoro-3-(trifluoromethyl)benzamide hydrochloride**

Using the procedure for the step A of example 7, the title compound was obtained. ESI MS m/e 440, M (free) + H^+; ^1H NMR (300 MHz, $CDCl_3$) δ 1.65-2.03 (m, 8 H), 2.49 (s, 3 H), 2.97-3.40 (m, 6 H), 3.67-3.81 (m, 1 H), 4.02-4.23 (m, 1 H), 5.15 (s, 1 H), 6.63-6.79

(m, 1 H), 7.19-7.31 (m, 1 H), 7.97-8.08 (m, 1 H), 8.13-8.20 (m, 1 H), 8.50-8.60 (m, 1 H), 13.74-13.88 (m, 1 H).

Example 15

***N*-(*cis*-4-{[6-(Dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-3-fluoro-4-(trifluoromethyl)benzamide hydrochloride**

Using the procedure for the step A of example 7, the title compound was obtained. ESI MS m/e 462, M (free) + Na^+; ^1H NMR (300 MHz, $CDCl_3$) δ 1.64-2.06 (m, 8 H), 2.49 (s, 3 H), 2.97-3.39 (m, 6 H), 3.67-3.81 (m, 1 H), 4.02-4.23 (m, 1 H), 5.15 (s, 1 H), 6.76-6.95 (m, 1 H), 7.52-7.81 (m, 2 H), 8.47-8.62 (m, 1 H), 13.71-13.85 (m, 1 H).

Example 16

3-Chloro-*N*-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-4-(trifluoromethoxy)benzamide hydrochloride

Using the procedure for the step A of example 7, the title compound was obtained. ESI MS m/e 494, M (free) + Na^+; ^1H NMR (300 MHz, $CDCl_3$) δ 1.60-2.06 (m, 8 H), 2.49 (s, 3 H) 2.95-3.40 (m, 6 H), 3.70-3.78 (m, 1 H), 4.02-4.24 (m, 1 H), 5.15 (s, 1 H), 6.59-6.72 (m, 1 H), 7.34-7.41 (m, 1 H), 7.71-7.80 (m, 1 H), 7.96-8.04 (m, 1 H), 8.48-8.62 (m, 1 H), 13.75-13.90 (m, 1 H).

Example 17

***N*-(*cis*-4-{[6-(Dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-3-(trifluoromethyl)-benzamide hydrochloride**

Using the procedure for the step A of example 7, the title compound was obtained. ESI MS m/e 444, M (free) + Na^+; ^1H NMR (300 MHz, $CDCl_3$) δ 1.66-2.17 (m, 8 H), 2.49 (s, 3 H), 2.97-3.38 (m, 6 H), 3.65-3.80 (m, 1 H), 4.06-4.23 (m, 1 H), 5.15 (s, 1 H), 6.59-6.71 (m, 1 H), 7.52-7.62 (m, 1 H), 7.69-7.80 (m, 1 H), 7.93-8.02 (m, 1 H), 8.13 (s, 1 H), 8.51-8.68 (m, 1 H), 13.81-13.96 (m, 1 H).

Example 18

***N*-(*cis*-4-{[6-(Dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-3-(trifluoromethoxy)benzamide hydrochloride**

Using the procedure for the step A of example 7, the title compound was obtained. ESI MS m/e 438, M (free) + Na^+; ^1H NMR (300 MHz, $CDCl_3$) δ 1.68-2.06 (m, 8 H), 2.49 (s, 3 H), 2.94-3.44 (m, 6 H) ,3.67-3.81 (m, 1 H), 4.03-4.23 (m, 1 H), 5.14 (s, 1 H), 6.51-6.66 (m, 1 H), 7.29-7.37 (m, 1 H), 7.42-7.53 (m, 1 H), 7.65-7.74 (m, 2 H), 8.46-8.69 (m, 1 H), 13.79-13.95 (m, 1 H).

Example 19

***N*-(*cis*-4-{[6-(Dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-4-(trifluoromethyl)benzamide hydrochloride**

Using the procedure for the step A of example 7, the title compound was obtained. ESI MS m/e 422, M (free) + H^+; ^1H NMR (300 MHz, $CDCl_3$) δ 1.64-2.06 (m, 8 H), 2.49 (s, 3 H), 2.97-3.39 (m, 6 H), 3.65-3.81 (m, 1 H), 4.05-4.23 (m, 1 H), 5.15 (s, 1 H), 6.71-6.84 (m, 1 H), 7.69 (d, J = 8.2 Hz, 2 H), 7.95 (d, J = 8.2 Hz, 2 H), 8.48-8.62 (m, 1 H).

Example 20

***N*-(*cis*-4-{[6-(Dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-4-(trifluoromethoxy)benzamide hydrochloride**

Using the procedure for the step A of example 7, the title compound was obtained. ESI MS m/e 460, M (free) + Na^+; ^1H NMR (300 MHz, $CDCl_3$) δ 1.63-2.02, (m, 8 H), 2.48 (s, 3 H), 2.89-3.42 (m, 6 H), 3.66-3.78 (m, 1 H), 4.03-4.25 (m, 1 H), 5.14 (s, 1 H), 6.72-6.86 (m, 1 H), 7.26 (d, J = 7.6 Hz, 2 H), 7.89 (d, J = 8.9 Hz, 2 H), 8.45-8.59 (m, 1 H).

Example 21

3,5-Dichloro-*N*-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-

yl]amino}cyclohexyl)-benzamide hydrochloride

Using the procedure for the step A of example 7, the title compound was obtained. ESI MS m/e 444, M (free) + Na^+; ^1H NMR (300 MHz, $CDCl_3$) δ 1.65-2.02 (m, 8 H), 2.49 (s, 3 H), 2.93-3.42 (m, 6 H), 3.68-3.79 (m, 1 H), 4.02-4.19 (m, 1 H), 5.14 (s, 1 H), 6.47-6.57 (m, 1 H), 7.45-7.48 (m, 1 H), 7.68 (d, J = 1.8 Hz, 2 H), 8.52-8.65 (m, 1 H).

Example 22

***N*-(*cis*-4-{[6-(Dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-fluorobenzamide hydrochloride**

Using the procedure for the step A of example 7, the title compound was obtained. ESI MS m/e 394, M (free) + Na^+; ^1H NMR (300 MHz, $CDCl_3$) δ 1.65-2.06 (m, 8 H), 2.48 (s, 3 H), 2.93-3.40 (m, 6 H), 3.63-3.71 (m, 1 H), 4.08-4.24 (m, 1 H), 5.12 (s, 1 H), 6.69-6.85 (m, 1 H), 7.06-7.30 (m, 2 H), 7.39-7.53 (m, 1 H), 7.95-8.05 (m, 1 H), 8.51-8.61 (m, 1 H).

Example 23

***N*-(*cis*-4-{[6-(Dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-3-fluorobenzamide hydrochloride**

Using the procedure for the step A of example 7, the title compound was obtained. ESI MS m/e 394, M (free) + Na^+; ^1H NMR (300 MHz, $CDCl_3$) δ 1.64-2.05 (m, 8 H), 2.49 (s, 3 H), 2.99-3.45 (m, 6 H), 3.66-3.77 (m, 1 H), 4.04-4.23 (m, 1 H), 5.14 (s, 1 H), 6.40-6.53 (m, 1 H), 7.13-7.22 (m, 1 H), 7.34-7.45 (m, 1 H), 7.52-7.58 (m, 2 H), 8.52-8.62 (m, 1 H).

Example 24

3-Chloro-*N*-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-benzamide hydrochloride

Using the procedure for the step A of example 7, the title compound was obtained.

ESI MS m/e 388, M (free) + H^+; ^1H NMR (300 MHz, $CDCl_3$) δ 1.68-2.03 (m, 8 H), 2.49 (s, 3 H), 2.97-3.37 (m, 6 H), 3.66-3.77 (m, 1 H), 4.02-4.21 (m, 1 H), 5.14 (s, 1 H), 6.48-6.57 (m, 1 H), 7.32-7.49 (m, 2 H), 7.63-7.69 (m, 1 H), 7.81-7.85 (m, 1 H), 8.53-8.62 (m, 1 H), 13.86-13.97 (m, 1 H).

Example 25

4-Chloro-*N*-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-benzamide hydrochloride

Using the procedure for the step A of example 7, the title compound was obtained. ESI MS m/e 388, M (free) + H^+; ^1H NMR (300 MHz, $CDCl_3$) δ 1.67-2.07 (m, 8 H), 2.49 (s, 3 H), 2.98-3.38 (m, 6 H), 3.67-3.79 (m, 1 H), 4.01-4.21 (m, 1 H), 5.14 (s, 1 H), 6.42-6.55 (m, 1 H), 7.37-7.43 (m, 2 H), 7.73-7.80 (m, 2 H), 8.52-8.63 (m, 1 H), 13.82-13.98 (m, 1 H).

Example 26

***N*-(*cis*-4-{[6-(Dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-3-fluoro-5-(trifluoromethyl)benzamide hydrochloride**

Using the procedure for the step A of example 7, the title compound was obtained. ESI MS m/e 462, M (free) + Na^+; ^1H NMR (300 MHz, $CDCl_3$) δ 1.70-2.05 (m, 8 H), 2.48 (s, 3 H), 2.93-3.45 (m, 6 H), 3.67-3.79 (m, 1 H), 4.04-4.23 (m, 1 H), 5.15 (s, 1 H), 6.71-6.84 (m, 1 H), 7.40-7.47 (m, 1 H), 7.72-7.79 (m, 1 H), 7.90 (s, 1 H), 8.49-8.63 (m, 1 H).

Example 27

***N*-(*cis*-4-{[6-(Dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-3,5-bis-(trifluoromethyl)benzamide hydrochloride**

Using the procedure for the step A of example 7, the title compound was obtained. ESI MS m/e 512, M (free) + Na^+; ^1H NMR (300 MHz, $CDCl_3$) δ 1.66-2.09 (m, 8 H), 2.48 (s, 3 H), 2.91-3.44 (m, 6 H), 3.67-3.83 (m, 1 H), 4.04-4.27 (m, 1 H), 5.15 (s, 1 H), 6.92-7.05 (m, 1 H), 7.98 (s, 1 H), 8.32 (s, 2 H), 8.50-8.64 (m, 1 H).

Example 28

***N*-[*cis*-4-({[6-(Dimethylamino)-2-methylpyrimidin-4-yl]amino}methyl)cyclohexyl]-3,4-difluorobenzamide hydrochloride**

Using the procedure for the step F of example 3, the title compound was obtained.

ESI MS m/e 404, M (free) + H^+; ^1H NMR (300 MHz, $CDCl_3$) δ 1.50-2.08 (m, 9 H), 2.46 (s, 3 H), 2.88 (s, 8 H), 4.43-4.58 (m, 1 H), 5.06 (s, 1 H), 7.10-7.35 (m, 2 H), 7.88-8.08 (m, 2 H), 8.58-8.78 (m, 1 H), 13.44-13.62 (m, 1 H).

Example 29

***N*-[(*cis*-4-{[6-(Dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)methyl]-3,4-difluorobenzamide hydrochloride**

Using the procedure for the step C of example 4, the title compound was obtained.

ESI MS m/e 404, M (free) + H^+; ^1H NMR (300 MHz, $CDCl_3$) δ 1.50-2.01 (m, 9 H), 2.47 (s, 3 H), 2.89-3.56 (m, 8 H), 3.66-3.86 (m, 1 H), 5.12 (s, 1 H), 6.82-6.98 (m, 1 H), 7.11-7.32 (m, 1 H), 7.72-7.97 (m, 2 H), 8.61-8.75 (m, 1 H), 13.61-13.89 (m, 1 H).

Example 30

3,4-Difluoro-*N*-(*cis*-4-{[2-methyl-6-(methylamino)pyrimidin-4-yl]amino}cyclohexyl)-benzamide hydrochloride

Step A: Synthesis of (6-chloro-2-methyl-pyrimidin-4-yl)-methyl-amine.

To a solution of 4,6–dichloro-2-methyl-pyrimidine obtained in step A of example 5 (11.1 g) in THF (110 mL) were added iPr_2NEt (14.2 mL) and 40% aqueous $MeNH_2$ (10.1 mL). The mixture was stirred at ambient temperature for 7 hr and concentrated under reduced pressure. To the residue was added saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtered, concentrated under reduced pressure, and dried under reduced pressure to give (6-chloro-2-methyl-pyrimidin-4-yl)-methyl-amine (10.7 g).

ESI MS m/e 157, M^+; ^1H NMR (200 MHz, $CDCl_3$) δ 2.48 (s, 3 H), 2.93 (d, J = 5.2 Hz, 3

H), 5.20-5.70 (m, 1 H), 6.18 (s, 1 H).

Step B: Synthesis of 3,4-difluoro-*N*-(*cis*-4-{[2-methyl-6-(methylamino)pyrimidin-4-yl]amino}-cyclohexyl)-benzamide hydrochloride.

Using the procedure for the step C of example 5, the title compound was obtained. ESI MS m/e 376, M (free) + H^+; ^1H NMR (300 MHz, $CDCl_3$) δ 1.58-2.13 (m, 8 H), 2.37 (s, 3 H), 2.82-3.19 (m, 3 H), 3.56-3.86 (m, 1 H), 3.98-4.27 (m, 1 H), 5.03-5.30 (m, 1 H), 6.07-6.52 (m, 1 H), 6.71-6.96 (m, 1 H), 7.11-7.33 (m, 1 H), 7.49-7.82 (m, 2 H), 8.34-8.60 (m, 1 H).

Example 31

3-Chloro-4-fluoro-*N*-(*cis*-4-{[2-methyl-6-(methylamino)pyrimidin-4-yl]amino}cyclohexyl)-benzamide hydrochloride

Step A: Synthesis of *N*-(*cis*-4-amino-cyclohexyl)-3-chloro-4-fluoro-benzamide.

To a solution of 3-chloro-4-fluoro-benzoic acid (26.9 g) and *cis*-(4-amino-cyclohexyl)-carbamic acid *tert*-butyl ester (30.0 g) in DMF (300 mL) were added Et_3N (46.8 mL), HOBt-H_2O (32.2 g), and EDC-HCl (29.5 g). The mixture was stirred at ambient temperature for 20 hr. To the mixture was added water (1.20 L) and the aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. A solution of the residue in EtOAc (650 mL) was cooled on an ice-bath and 4 M hydrogen chloride in EtOAc (325 mL) was added. The mixture was stirred at ambient temperature for 16 hr and concentrated under reduced pressure. The residue was dissolved in 1 M aqueous NaOH (300 mL) and the aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtered, concentrated under reduced pressure, and dried under reduced pressure to give *N*-(*cis*-4-amino-cyclohexyl)-3-chloro-4-fluoro-benzamide (44.4 g).

ESI MS m/e 271, M (free) + H^+; ^1H NMR (300 MHz, $CDCl_3$) δ 1.37-1.92 (m, 8 H), 2.94-3.08 (m, 1 H), 4.06-4.22 (m, 1 H), 6.13-6.31 (m, 1 H), 7.19 (t, J = 8.5 Hz, 1 H), 7.61-7.70

(m, 1 H), 7.79-7.87 (m, 1 H).

Step B: Synthesis of 3-chloro-4-fluoro-*N*-(*cis*-4-{[2-methyl-6-(methylamino)pyrimidin-4-yl]-amino}cyclohexyl)-benzamide hydrochloride.

To a solution of *N*-(*cis*-4-amino-cyclohexyl)-3-chloro-4-fluoro-benzamide (472 mg) in BuOH (1 mL) was added (6-chloro-2-methyl-pyrimidin-4-yl)-methyl-amine obtained in step A of example 30 (250 mg). The mixture was heated in a microwave synthesizer at 220°C for 20 min. To the mixture was added saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtrated, concentrated under reduced pressure, and purified by medium-pressure liquid chromatography (NH-silica gel, 50% EtOAc in hexane) to give 3-chloro-4-fluoro-*N*-(*cis*-4-{[2-methyl-6-(methylamino)pyrimidin-4-yl]-amino}cyclohexyl)-benzamide. To a solution of the above material in EtOAc (10 mL) was added 4 M hydrogen chloride in EtOAc (0.2 mL). The mixture was stirred at ambient temperature for 1 hr and concentrated under reduced pressure. A suspension of the residue in Et_2O (12 mL) was stirred at ambient temperature for 2 hr. The precipitate was collected by filtration, washed with Et_2O, and dried at 70°C under reduced pressure to give 3-chloro-4-fluoro-*N*-(*cis*-4-{[2-methyl-6-(methylamino)pyrimidin-4-yl]-amino}cyclohexyl)-benzamide hydrochloride (64 mg).

ESI MS m/e 392, M (free) + H^+; ^1H NMR (300 MHz, DMSO-d_6) δ 1.54-1.90 (m, 8 H), 2.29-2.43 (m, 3 H), 2.74-2.94 (m, 3 H), 3.80-3.96 (m, 2 H), 5.44-5.64 (m, 1 H), 7.53 (t, J = 8.9 Hz, 1 H), 7.86-7.94 (m, 2 H), 8.07-8.13 (m, 2 H), 8.31-8.47 (m, 1 H).

Example 32

***N*-(*cis*-4-{[6-(Dimethylamino)-2-ethylpyrimidin-4-yl]amino}cyclohexyl)-3,4-difluorobenzamide hydrochloride**

Step A: Synthesis of (2,6-dichloro-pyrimidin-4-yl)-dimethyl-amine.

To a solution of 2,4,6-trichloro-pyrimidine (10.0 g) in THF (50 mL) were added 50% aqueous Me_2NH (4.92 g) and iPr_2NEt (8.46 g). The mixture was stirred at ambient

temperature for 1.5 hr and concentrated under reduced pressure. The residue was poured into saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtered, concentrated under reduced pressure, and purified flash chromatography (NH-silica gel, 3% EtOAc in hexane) to give (2,6-dichloro-pyrimidin-4-yl)-dimethyl-amine (6.03 g).

ESI MS m/e 192, $M + H^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 2.77-3.46 (m, 6 H), 6.34 (s, 1 H).

Step B: Synthesis of (6-chloro-2-ethyl-pyrimidin-4-yl)-dimethyl-amine.

A solution of $ZnBr_2$ (3.87 g) in THF (60 mL) was cooled to –60°C and 1 M EtMgBr in THF (17.2 mL) was added. The mixture was stirred at –60°C for 1 hr and warmed to ambient temperature. To the mixture were added tetrakis-(triphenylphosphine)-palladium (903 mg) and (2,6-dichloro-pyrimidin-4-yl)-dimethyl-amine in THF (60 mL) and the mixture was stirred at reflux for 5 days. To the mixture was added saturated aqueous NH_4Cl and the aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtered, concentrated under reduced pressure, and purified by medium-pressure liquid chromatography (silica gel, 17% to 33% EtOAc in hexane) to give (2-chloro-6-ethyl-pyrimidin-4-yl)-dimethyl-amine (352 mg) and (6-chloro-2-ethyl-pyrimidin-4-yl)-dimethyl-amine (622 mg).

(2-chloro-6-ethyl-pyrimidin-4-yl)-dimethyl-amine;

ESI MS m/e 208, M (free) + Na^+; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, J = 7.6 Hz, 3 H), 2.54-2.66 (m, 2 H), 3.11 (s, 6 H), 6.15 (s, 1 H).

(6-chloro-2-ethyl-pyrimidin-4-yl)-dimethyl-amine;

ESI MS m/e 186, $M + H^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (t, J = 7.6 Hz, 3 H), 2.74 (q, J = 7.7 Hz, 2 H), 3.10 (s, 6 H), 6.24 (s, 1 H).

Step C: Synthesis of *N*-(*cis*-4-{[6-(dimethylamino)-2-ethylpyrimidin-4-yl]amino}cyclohexyl)-3,4-difluorobenzamide hydrochloride.

Using the procedure for the step C of example 5, the title compound was obtained.

ESI MS m/e 404, M (free) + H^+; ^1H NMR (300 MHz, $CDCl_3$) δ 1.37 (t, J = 7.5 Hz, 3 H), 1.64-2.03 (m, 8 H), 2.76 (q, J = 7.5 Hz, 2 H), 2.97-3.42 (m, 6 H), 3.65-3.80 (m, 1 H), 4.02-

4.21 (m, 1 H), 5.14 (s, 1 H), 6.42-6.66 (m, 1 H), 7.12-7.27 (m, 1 H), 7.45-7.60 (m, 1 H), 7.65-7.81 (m, 1 H), 8.60-8.73 (m, 1 H), 13.61-13.77 (m, 1 H).

Example 33

***N*-(*cis*-4-{[2,6-bis(Dimethylamino)pyrimidin-4-yl]amino}cyclohexyl)-3,4-difluorobenzamide hydrochloride**

Step A: Synthesis of 6-chloro-*N*,*N*,*N*',*N*'-tetramethyl-pyrimidine-2,4-diamine.

To a suspension of (2,6-dichloro-pyrimidin-4-yl)-dimethyl-amine obtained in step A of example 32 (1.60 g) in IPA (2 mL) was added 50% aqueous Me_2NH (789 mg). The mixture was stirred at reflux for 3.5 hr in a sealed tube. The mixture was poured into saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtered, concentrated under reduced pressure, and purified by medium-pressure liquid chromatography (silica gel, 20% EtOAc in hexane) to give 2-chloro-*N*,*N*,*N*',*N*'-tetramethyl-pyrimidine-4,6-diamine (203 mg) and 6-chloro-*N*,*N*,*N*',*N*'-tetramethyl-pyrimidine-2,4-diamine (1.43 g).

2-chloro-*N*,*N*,*N*',*N*'-tetramethyl-pyrimidine-4,6-diamine;

ESI MS m/e 201, M (free) + H^+; ^1H NMR (300 MHz, $CDCl_3$) δ 3.05 (s, 12 H), 5.15 (s, 1 H).

6-chloro-*N*,*N*,*N*',*N*'-tetramethyl-pyrimidine-2,4-diamine;

ESI MS m/e 201, M + H^+; ^1H NMR (300 MHz, $CDCl_3$) δ 3.04 (s, 6 H), 3.13 (s, 6 H), 5.76 (s, 1 H).

Step B: Synthesis of *N*-(*cis*-4-{[2,6-bis(dimethylamino)pyrimidin-4-yl]amino}cyclohexyl)-3,4-difluorobenzamide hydrochloride

Using the procedure for the step C of example 5, the title compound was obtained.

ESI MS m/e 419, M (free) + H^+; ^1H NMR (300 MHz, $CDCl_3$) δ 1.58-2.16 (m, 8 H), 2.97-3.45 (m, 12 H), 3.62-3.74 (m, 1 H), 4.03-4.21 (m, 1 H), 4.81 (s, 1 H), 6.76-6.90 (m, 1 H), 7.13-7.26 (m, 1 H), 7.55-7.64 (m, 1 H), 7.70-7.79 (m, 1 H), 8.57-8.70 (m, 1 H), 11.86-11.94 (m, 1 H).

Example 34

***N*-(*cis*-4-{[2-(Ethylamino)pyrimidin-4-yl]amino}cyclohexyl)-3,4-difluorobenzamide hydrochloride**

Step A: Synthesis of (4-chloro-pyrimidin-2-yl)-ethyl-amine.

To a solution of 2,4-dichloro-pyrimidine (5.00 g) in THF (50 mL) was added 70% aqueous $EtNH_2$ (5.40 g). The mixture was stirred at ambient temperature for 1 hr and concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ and the solution was poured into saturated aqueous $NaHCO_3$. The two layers were separated and the aqueous layer was extracted with $CHCl_3$ (twice). The combined organic layer was dried over $MgSO_4$, filtered, concentrated under reduced pressure, and purified by flash chromatography (silica gel, 17% to 50% EtOAc in hexane) to give (2-chloro-pyrimidin-4-yl)-ethyl-amine (3.69 g) and (4-chloro-pyrimidin-2-yl)-ethyl-amine (1.28 g).

(2-chloro-pyrimidin-4-yl)-ethyl-amine;

ESI MS m/e 157, M^+; ^1H NMR (500 MHz, $CDCl_3$) δ 1.26 (t, J = 7.3 Hz, 3 H), 3.16-3.62 (m, 2 H), 4.80-5.95 (m, 1 H), 6.23 (d, J = 5.8 Hz, 1 H), 8.02-8.22 (m, 1 H).

(4-chloro-pyrimidin-2-yl)-ethyl-amine;

CI MS m/e 158, $M + H^+$; ^1H NMR (500 MHz, $CDCl_3$) δ 1.23 (t, J = 7.5 Hz, 3 H), 3.42-3.49 (m, 2 H), 5.30-5.62 (m, 1 H), 6.54 (d, J = 5.2 Hz, 1 H), 8.02-8.22 (m, 1 H).

Step B: Synthesis of *N*-(*cis*-4-{[2-(ethylamino)pyrimidin-4-yl]amino}cyclohexyl)-3,4-difluorobenzamide hydrochloride

Using the procedure for the step C of example 5, the title compound was obtained.

ESI MS m/e 376, M (free) + H^+; ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (t, J = 7.1 Hz, 3 H), 1.61 (s, 8 H), 3.31-3.56 (m, 2 H), 4.05-4.47 (m, 2 H), 6.31-6.56 (m, 1 H), 6.75-6.95 (m, 1 H), 7.07–7.34 (m, 2 H), 7.48-7.87 (m, 3 H), 8.01-8.24 (m, 1 H), 12.39-12.52 (m, 1 H).

Example 35

***N*-[*cis*-4-({2-[Ethyl(methyl)amino]pyrimidin-4-yl}amino)cyclohexyl]-3,4-difluorobenzamide hydrochloride**

Step A: Synthesis of (4-chloro-pyrimidin-2-yl)-ethyl-methyl-amine.

To a solution of 2,4-dichloro-pyrimidine (5.00 g) in THF (50 mL) was added ethyl-methyl-amine (2.08 g). The mixture was stirred at ambient temperature for 1 hr and concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ and the solution was poured into saturated aqueous $NaHCO_3$. The two layers were separated and the aqueous layer was extracted with $CHCl_3$ (twice). The combined organic layer was dried over $MgSO_4$, filtered, concentrated under reduced pressure, and purified by flash chromatography (silica gel, 17% to 50% EtOAc in hexane) to give (2-chloro-pyrimidin-4-yl)-ethyl-methyl-amine (4.49 g) as (4-chloro-pyrimidin-2-yl)-ethyl-methyl-amine (0.91 g).

(2-chloro-pyrimidin-4-yl)-ethyl-methyl-amine;

CI MS m/e 172, M (free) + H^+; ^1H NMR (500 MHz, $CDCl_3$) δ 1.18 (t, J = 3.0 Hz, 3 H), 3.06 (brs, 3 H), 3.35-3.70 (m, 2 H), 6.29 (d, J = 4.8 Hz, 1 H), 7.99(d, J = 6.1 Hz, 1 H).

(4-chloro-pyrimidin-2-yl)-ethyl-methyl-amine;

CI MS m/e 172, M + H^+; ^1H NMR (500 MHz, $CDCl_3$) δ 1.17 (t, J = 3.0 Hz, 3 H), 3.10 (s, 3 H), 3.66 (q, J = 7.0 Hz, 2 H), 6.45 (d, J = 5.0 Hz, 1 H), 8.14 (d, J = 5.0 Hz, 1 H).

Step B: Synthesis of *N*-[*cis*-4-({2-[ethyl(methyl)amino]pyrimidin-4-yl}amino)cyclohexyl]-3,4-difluorobenzamide hydrochloride

Using the procedure for the step C of example 5, the title compound was obtained.

ESI MS m/e 390, M (free) + H^+; ^1H NMR (300 MHz, $CDCl_3$) δ 1.11-1.29 (m, 3 H), 1.63-2.20 (m, 8 H), 3.23 (brs, 3 H), 3.61-3.76 (m, 2 H), 4.06-4.42 (m, 2 H), 6.53-6.68 (m, 1 H), 6.88-7.24 (m, 2 H), 7.39-7.52 (m, 1 H), 7.59-7.86 (m, 2 H), 8.39-8.54 (m, 1 H), 12.26-12.44 (m, 1 H).

Example 36

3,4-Difluoro-*N*-[*cis*-4-({2-[(2-hydroxyethyl)(methyl)amino]pyrimidin-4-yl}amino)-cyclohexyl]benzamide hydrochloride

Step A: Synthesis of 2-[(4-chloro-pyrimidin-2-yl)-methyl-amino]-ethanol.

To a solution of 2,4-dichloro-pyrimidine (5.00 g) in THF (50 mL) was added 2-methylamino-ethanol (2.65 g). The mixture was stirred at ambient temperature for 1 hr and concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ and the solution was poured into saturated aqueous $NaHCO_3$. The two layers were separated and the aqueous layer was extracted with $CHCl_3$ (twice). The combined organic layer was dried over $MgSO_4$, filtered, concentrated under reduced pressure, and purified by flash chromatography (silica gel, 17% to 50% EtOAc in hexane) to give 2-[(2-chloro-pyrimidin-4-yl)-methyl-amino]-ethanol (3.50 g) and 2-[(4-chloro-pyrimidin-2-yl)-methyl-amino]-ethanol (827 mg).

2-[(2-chloro-pyrimidin-4-yl)-methyl-amino]–ethanol;

ESI MS m/e 188, M (free) + H^+; ^1H NMR (500 MHz, $CDCl_3$) δ 2.91 (brs, 3 H), 3.13 (s, 3 H), 3.64-3.92 (m, 4 H), 6.46-6.49 (m, 1 H), 7.99 (d, J = 6.1 Hz, 1 H).

2-[(4-chloro-pyrimidin-2-yl)-methyl-amino]–ethanol;

ESI MS m/e 210, M + Na^+; ^1H NMR (500 MHz, $CDCl_3$) δ 3.23 (s, 3 H), 3.76-3.92 (m, 4 H), 6.52 (d, J = 5.2 Hz, 1 H), 8.12 (d, J = 4.6 Hz, 1 H).

Step B: Synthesis of 3,4-difluoro-*N*-[*cis*-4-({2-[(2-hydroxyethyl)(methyl)amino]pyrimidin-4–yl}amino)-cyclohexyl]benzamide hydrochloride

Using the procedure for the step C of example 5, the title compound was obtained.

ESI MS m/e 406, M (free) + H^+; ^1H NMR (300 MHz, DMSO-d_6) δ 1.59-1.96 (m, 8 H), 3.16 (s, 3 H) 3.57-3.71 (m, 2 H), 3.80-4.07 (m, 3 H), 4.20-4.30 (m, 1 H), 6.20-6.34 (m, 1 H), 7.49-7.80 (m, 3 H), 7.88-7.99 (m, 1 H), 8.31-8.40 (m, 1 H), 8.64-8.79 (m, 1 H).

Example 37

3-Chloro-4-fluoro-*N*-{*cis*-4-[(2-methyl-6-piperidin-1-ylpyrimidin-4-yl)amino]cyclohexyl}-benzamide hydrochloride

To a solution of 4,6-dichloro-2-methyl-pyrimidine obtained in step A of example 5 (3.00 g) in THF (30 mL) were added *N*-(*cis*-4-amino-cyclohexyl)-3-chloro-4-fluoro-

benzamide obtained in step A of example 31 (5.98 g) and $iPrNEt_2$ (3.85 mL). The mixture was stirred at reflux for 60 hr and poured into saturated aqueous $NaHCO_3$. The aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtrated, concentrated under reduced pressure, and purified by medium-pressure liquid chromatography (NH-silica gel, 20% EtOAc in hexane) to give 3-chloro-N-[*cis*-4-(6-chloro-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-4-fluoro-benzamide (6.34 g). To a solution of above solid (250 mg) in BuOH (1 mL) were added piperidine (80 mg) and $iPrNEt_2$ (121 mg). The mixture was heated in a microwave synthesizer at 220°C for 10 min and 230°C for 20 min and poured into saturated aqueous $NaHCO_3$. The aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtrated, concentrated under reduced pressure, and purified by medium-pressure liquid chromatography (NH-silica gel, 20% EtOAc in hexane) to give 3-chloro-4-fluoro-*N*-{*cis*-4-[(2-methyl-6-piperidin-1-ylpyrimidin-4-yl)amino]cyclohexyl}-benzamide. To a solution of the above material in EtOAc (10 mL) was added 4 M hydrogen chloride in EtOAc (0.2 mL). The mixture was stirred at ambient temperature for 1 hr and concentrated under reduced pressure. A suspension of the residue in Et_2O (12 mL) was stirred at ambient temperature for 2 hr. The precipitate was collected by filtration, washed with Et_2O, and dried at 70°C under reduced pressure to give 3-chloro-4-fluoro-*N*-{*cis*-4-[(2-methyl-6-piperidin-1-ylpyrimidin-4-yl)amino]cyclohexyl}-benzamide hydrochloride (6 mg).

ESI MS m/e 446, M (free) + H^+; ^1H NMR (300 MHz, $CDCl_3$) δ 1.28-2.10 (m, 14 H), 2.46 (s, 3 H), 2.92-3.11 (m, 1 H), 3.27-3.89 (m, 4 H), 4.00-4.21 (m, 1 H), 5.16-5.31 (m, 1 H), 6.69-6.88 (m, 1 H), 7.13-7.27 (m, 1 H), 7.60-8.03 (m, 2 H), 8.40-8.55 (m, 1 H).

Example 38

3-Chloro-4-fluoro-*N*-(*cis*-4-{[6-(1*H*-imidazol-1-yl)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-benzamide dihydrochloride

Using the procedure for the step A of example 37, the title compound was obtained.

ESI MS m/e 451, M (free) + Na^+; ^1H NMR (300 MHz, $CDCl_3$) δ 1.69-2.21 (m, 8 H), 2.56-2.87 (m, 3 H), 4.04-4.58 (m, 2 H), 6.41-6.70 (m, 1 H), 7.10-7.25 (m, 1 H), 7.42-7.51 (m, 1 H), 7.58-7.80 (m, 1 H), 7.84-8.22 (m, 3 H).

Example 39

3-Chloro-4-fluoro-*N*-{*cis*-4-[(2-methyl-6-morpholin-4-ylpyrimidin-4-yl)amino]cyclohexyl}-benzamide hydrochloride

Using the procedure for the step A of example 37, the title compound was obtained. ESI MS m/e 470, M (free) + Na^+; ^1H NMR (300 MHz, $CDCl_3$) δ 1.65-2.02 (m, 8 H), 2.49 (s, 3 H), 3.58-3.92 (m, 9 H), 4.03-4.22 (m, 1 H), 5.25 (s, 1 H), 6.51-6.62 (m, 1 H), 7.18 (t, J = 8.5 Hz, 1 H), 7.67-7.74 (m, 1 H), 7.91-7.96 (m, 1 H), 8.63-8.75 (m, 1 H).

Example 40

3-Chloro-4-fluoro-*N*-{cis-4-[(2-methyl-6-pyrrolidin-1-ylpyrimidin-4-yl)amino]cyclohexyl}-benzamide hydrochloride

Using the procedure for the step A of example 37, the title compound was obtained. ESI MS m/e 432, M (free) + H^+; ^1H NMR (300 MHz, $CDCl_3$) δ 1.41-2.24 (m, 12 H), 2.48 (s, 3 H), 3.09-3.56 (m, 3 H), 3.60-3.78 (m, 2 H), 3.99-4.18 (m, 1 H), 5.02 (s, 1 H), 6.52-6.66 (m, 1 H), 7.18 (t, J = 8.6 Hz, 1 H), 7.63-7.77 (m, 1 H), 7.88-7.99 (m, 1 H), 8.40-8.55 (m, 1 H).

Example 41

3-Chloro-4-fluoro-*N*-(*cis*-4-{[2-methyl-6-(4-methylpiperazin-1-yl)pyrimidin-4-yl]amino}-cyclohexyl)benzamide dihydrochloride

Using the procedure for the step A of example 37, the title compound was obtained. ESI MS m/e 461, M (free) + H^+; ^1H NMR (300 MHz, DMSO-d_6) δ 1.63-1.88 (m, 8 H), 2.37-2.46 (m, 3 H), 2.73-2.83 (m, 3 H), 2.97-3.15 (m, 2 H), 3.24-3.62 (m, 6 H), 3.78-4.01 (m, 2 H), 5.99 (s, 1 H), 7.52 (t, J = 8.9 Hz, 1 H), 7.81-7.97 (m, 1 H), 8.04-8.16 (m, 2 H),

8.40-8.54 (m, 1 H).

Example 42

N^4-(*cis*-4-{[4-Bromo-2-(trifluoromethoxy)benzyl]amino}cyclohexyl)-N^2,N^2-dimethylpyrimidine-2,4-diamine dihydrochloride

Step A: Synthesis of (4-chloro-pyrimidin-2-yl)-dimethyl-amine.

To a solution of 2,4-dichloro-pyrimidine (15.0 g) in THF (150 mL) was added 50% aqueous Me_2NH (22.7 g). The mixture was stirred at ambient temperature for 2 hr and poured into saturated aqueous $NaHCO_3$. The aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtrated, concentrated under reduced pressure, and purified by flash chromatography (NH-silica, 20% EtOAc in hexane) to give (2-chloro-pyrimidin-4-yl)-dimethyl-amine (8.66 g) and (4-chloro-pyrimidin-2-yl)-dimethyl-amine (0.87 g).

(2-chloro-pyrimidin-4-yl)-dimethyl-amine;

CI MS m/e 158, $M + H^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 3.12 (s, 6 H), 6.32 (d, J = 6.1 Hz, 1 H), 8.00 (d, J = 6.1 Hz, 1 H).

(4-chloro-pyrimidin-2-yl)-dimethyl-amine;

ESI MS m/e 157, M^+; ^1H NMR (300 MHz, $CDCl_3$) δ 3.21 (s, 6 H), 6.50 (d, J = 5.1 Hz, 1 H), 8.18 (d, J = 5.1 Hz, 1 H).

Step B: Synthesis of N^4-(*cis*-4-{[4-bromo-2-(trifluoromethoxy)benzyl]amino}cyclohexyl)-N^2,N^2-dimethylpyrimidine-2,4-diamine dihydrochloride.

A mixture of *N*-(*cis*-4-bromo-2-trifluoromethoxy-benzyl)-cyclohexane-1,4-diamine obtained in step B of example 1 (466 mg), (4-chloro-pyrimidin-2-yl)-dimethyl-amine (200 mg), and BuOH (1 mL) was stirred at reflux for 13 hr. The mixture was poured into saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtered, concentrated under reduced pressure, and purified by flash chromatography (NH-silica gel, 20% EtOAc

in) to give N^4-(*cis*-4-{[4-bromo-2-(trifluoromethoxy)benzyl]amino}-cyclohexyl)-N^2,N^2-dimethylpyrimidine-2,4-diamine. To a solution of the above material in EtOAc (2 mL) was added 4 M hydrogen chloride in EtOAc (10 mL). The mixture was stirred at ambient temperature for 1 hr and concentrated under reduced pressure. The residue was suspended in Et_2O (20 mL) and the suspension was stirred at ambient temperature for 4 hr. The precipitate was collected by filtration, washed with Et_2O, and dried under reduced pressure to give N^4-(*cis*-4-{[4-bromo-2-(trifluoromethoxy)benzyl]-amino}cyclohexyl)-N^2,N^2-dimethylpyrimidine-2,4-diamine dihydrochloride (294 mg).

ESI MS m/e 488, M (free) + H^+; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42-1.67 (m, 2 H), 2.03-2.39 (m, 6 H), 2.79-3.38 (m, 7 H), 4.13-4.36 (m, 3 H), 6.89-7.00 (m, 1 H), 7.42-7.46 (m, 1 H), 7.50-7.57 (m, 1 H), 7.90-8.01 (m, 1 H), 8.12 (d, J = 8.4 Hz, 1 H), 8.90-9.00 (m, 1 H), 9.98-10.18 (m, 2 H), 12.21-12.37 (m, 1 H).

Example 43

***N*-(*cis*-4-{[2-(Dimethylamino)-6-methylpyrimidin-4-yl]amino}cyclohexyl)-3,4-difluorobenzamide hydrochloride**

Step A: Synthesis of (4-chloro-6-methyl-pyrimidin-2-yl)-dimethyl-amine.

To a solution of 2,4-dichloro-6-methylpyrimidine (20.0 g) in THF (200 mL) was added 50% aqueous Me_2NH (13.3 g) and the mixture was stirred at ambient temperature for 24 hr. To the mixture was added saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtered, concentrated under reduced pressure, and purified flash chromatography (NH-silica gel, 5% to 16% EtOAc in hexane) to give (2-chloro-6-methyl-pyrimidin-4-yl)-dimethyl-amine (14.4 g) and (4-chloro-6-methyl-pyrimidin-2-yl)-dimethyl-amine (6.57 g).

(2-chloro-6-methyl-pyrimidin-4-yl)-dimethyl-amine;

ESI MS m/e 194, $M^+ + Na^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.34 (s, 3 H), 3.10 (s, 6 H), 6.16 (s, 1 H).

(4-chloro-6-methyl-pyrimidin-2-yl)-dimethyl-amine;

CI MS m/e 172, M + H^+; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.29 (s, 3 H), 3.16 (s, 6 H), 6.34 (s, 1 H).

Step B: Synthesis of *N*-(*cis*-4-{[2-(dimethylamino)-6-methylpyrimidin-4-yl]amino}cyclohexyl)-3,4-difluorobenzamide hydrochloride.

To a solution of *N*-(*cis*-4-amino-cyclohexylmethyl)-3,4-difluoro-benzamide (652 mg) in BuOH (1 mL) was added (4-chloro-6-methyl-pyrimidin-2-yl)-dimethyl-amine (400 mg). The mixture was stirred at reflux for 8 days. To the mixture was added saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtrated, concentrated under reduced pressure, and purified by medium-pressure liquid chromatography (NH-silica gel, 10% to 20% EtOAc in hexane) to give *N*-(*cis*-4-{[2-(dimethylamino)-6-methylpyrimidin-4-yl]amino}cyclohexyl)-3,4-difluorobenzamide. To a solution of the above material in EtOAc (5 mL) was added 4 M hydrogen chloride in EtOAc (10 mL). The mixture was stirred at ambient temperature for 1 hr and concentrated under reduced pressure. A suspension of the residue in Et_2O (20 mL) was stirred at ambient temperature for 4 hr. The precipitate was collected by filtration, washed with Et_2O, and dried at 80°C under reduced pressure to give *N*-(*cis*-4-{[2-(dimethylamino)-6-methylpyrimidin-4-yl]amino}cyclohexyl)-3,4-difluorobenzamide hydrochloride (507 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.62-2.21(m, 8 H), 2.39 (s, 3 H), 3.15-3.45 (m, 6 H), 4.09-4.43 (m, 2 H), 6.28-6.37 (m, 1 H), 7.06-7.24 (m, 1 H), 7.61-7.87 (m, 2 H), 8.24-8.37 (m, 1 H), 11.55-11.67 (m, 1 H).

Example 44

3-Chloro-*N*-(*cis*-4-{[2-(dimethylamino)pyrimidin-4-yl]amino}cyclohexyl)-4-fluorobenzamide hydrochloride

Using the procedure for the step B of example 31, the title compound was obtained. ESI MS m/e 392, M (free) + H^+; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.58-2.20 (m, 8 H), 3.07 (s,

6 H), 4.03-4.48 (m, 2 H), 6.52-6.73 (m, 1 H), 6.95-6.95 (m, 2 H), 7.36-7.51 (m, 1 H), 7.72-7.85 (m, 1 H), 7.94-8.05 (m, 1 H), 8.50-8.69 (m, 1 H), 12.20-12.41 (m, 1 H).

Example 45

3-Chloro-*N*-(*cis*-4-{[2-(dimethylamino)-6-methylpyrimidin-4-yl]amino}cyclohexyl)-4-fluorobenzamide hydrochloride

Using the procedure for the step B of example 31, the title compound was obtained. ESI MS m/e 406, M (free) + H^+; ^1H NMR (300 MHz, $CDCl_3$) δ 1.56-2.22 (m, 11 H), 3.05-3.45 (m, 6 H), 4.07-4.42 (m, 2 H), 6.25-6.40 (m, 1 H), 7.03-7.26 (m, 2 H), 7.73-8.07 (m, 2 H), 8.30-8.44 (m, 1 H), 11.51-11.64 (m, 1 H).

Example 46

3-Chloro-*N*-(*cis*-4-{[2-(dimethylamino)-5-methylpyrimidin-4-yl]amino}cyclohexyl)-4-fluorobenzamide hydrochloride

Step A: Synthesis of 4-chloro-2-dimethylamino-5-methylpyrimidine.

To a solution of 2,4-dichloro-5-methylpyrimidine (20.0 g) in THF (200 mL) was added 50% aqueous Me_2NH (13.3 g). The mixture was stirred at ambient temperature for 5 days and concentrated under reduced pressure. The residue was poured into saturated aqueous $NaHCO_3$. The aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtered, concentrated under reduced pressure, and purified by flash chromatography (NH-silica gel, 2% EtOAc in hexane) to give 2-chloro-4-dimethylamino-5-methylpyrimidine (19.9 g) and 4-chloro-2-dimethylamino-5-methylpyrimidine (1.53 g).

2-chloro-4-dimethylamino-5-methylpyrimidine;

ESI MS m/e 172, M + H^+ ; ^1H NMR (300 MHz, $CDCl_3$) δ 2.27 (s, 3 H), 3.15 (s, 6 H), 7.82 (s, 1 H).

4-chloro-2-dimethylamino-5-methylpyrimidine;

ESI MS m/e 194, M + Na^+; ^1H NMR (300 MHz, $CDCl_3$) δ 2.14 (s, 3 H), 3.15 (s, 6 H), 8.06

(s, 1 H).

Step B: Synthesis of 3-chloro-*N*-(*cis*-4-{[2-(dimethylamino)-5-methylpyrimidin-4-yl]amino}-cyclohexyl)-4-fluorobenzamide hydrochloride.

Using the procedure for the step B of example 31, the title compound was obtained. ESI MS m/e 406, M (free) + H^+; ^1H NMR (300 MHz, DMSO-d_6) δ 1.56-2.02 (m, 8 H), 2.04 (s, 3 H), 3.16 (s, 6 H), 3.90-4.18 (m, 2 H), 7.47-7.66 (m, 3 H), 7.91-8.00 (m, 1 H), 8.13-8.21 (m, 1 H), 8.28-8.36 (m, 1 H), 12.39-12.48 (m, 1 H).

Example 47

3-Chloro-*N*-(*cis*-4-{[6-(dimethylamino)-2-(trifluoromethyl)pyrimidin-4-yl]amino}cyclohexyl)-4-fluorobenzamide hydrochloride

Step A: Synthesis of 2-trifluoromethyl-pyrimidine-4,6-diol.

To a suspension of 60% NaH in oil (11.7 g) in toluene (98 mL) was added BuOH (21.8 g). The mixture was stirred at ambient temperature for 16 hr. To the mixture were added malonamide (10.0 g) and trifluoro-acetic acid ethyl ester (13.9 g). The mixture was stirred at 100°C for 3.5 hr and ambient temperature for 16 hr. The organic layer was extracted with water (two times) and the aqueous layer was filtrated through activated carbon. To the aqueous layer was added conc. HCl (pH 1) and the suspension was stirred at 4°C for 2 hr. The precipitate was collected by filtration and dried at 80°C under reduced pressure to give 2-trifluoromethyl-pyrimidine-4,6-diol (3.25 g).

ESI MS m/e 178, M - H^+; ^1H NMR (300 MHz, $CDCl_3$) δ 6.00 (s, 1 H), 12.48 (brs, 2 H).

Step B: Synthesis of (6-chloro-2-trifluoromethyl-pyrimidin-4-yl)-dimethyl-amine.

To a suspension of 2-trifluoromethyl-pyrimidine-4,6-diol (3.25 g) in $POCl_3$ (7.89 mL) was added Et_3N (5.00 mL). The mixture was stirred at 120°C for 3 hr, cooled to ambient temperature, and poured into ice water. The aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtrated, and concentrated under reduced pressure to give 4,6-dichloro-2-trifluoromethyl-pyrimidine. To the solution of the above material (1.00 g) in THF (10 mL) were added iPr_2NEt (0.98

mL) and 50% aqueous Me_2NH (0.48 mL). The mixture was stirred at ambient temperature for 60 hr. To the solution was added saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtered, concentrated under reduced pressure, and purified by medium-pressure liquid chromatography (silica gel, 5% to 25% EtOAc in hexane) to give (6-chloro-2-trifluoromethyl-pyrimidin-4-yl)-dimethyl-amine (728 mg).

ESI MS m/e 225 M^+; ^1H NMR (300 MHz, $CDCl_3$) δ 2.77-3.61 (m, 6 H), 6.50 (s, 1 H).

Step C: Synthesis of 3-chloro-*N*-(*cis*-4-{[6-(dimethylamino)-2-(trifluoromethyl)pyrimidin-4-yl]amino}cyclohexyl)-4-fluorobenzamide hydrochloride.

Using the procedure for the step B of example 31, the title compound was obtained.

ESI MS m/e 482, M (free) + H^+; ^1H NMR (300 MHz, $CDCl_3$) δ 1.66-2.08 (m, 8 H), 3.20 (s, 6 H), 3.68-3.83 (m, 1 H), 4.04-4.21 (m, 1 H), 5.30 (s, 1 H), 6.34-6.46 (m, 1 H), 7.18 (t, J = 8.5 Hz, 1 H), 7.63-7.73 (m, 2 H), 7.87-7.93 (m, 1 H).

Example 48

5-Bromo-furan-2-carboxylic acid [*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-amide trifluoroacetate

Step A: Synthesis of [*cis*-4-(6-chloro-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-carbamic acid tert-butyl ester.

To a solution of 4,6-dichloro-2-methyl-pyrimidine (4.87 g, 0.030 mol) in 50 mL MeOH were added DIEA (10.4 mL, 0.059 mol) and *cis*-(4-amino-cyclohexyl)-carbamic acid *tert*-butyl ester (6.4g, 0.030 mol). The mixture was stirred at reflux overnight and the solvent concentrated. The resulting oil was subjected to chromatography (0-70 % ethyl acetate in hexanes) to yield [*cis*-4-(6-chloro-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-carbamic acid *tert*-butyl ester (9.7 g, 0.028mol, 95%) as a white solid.

ESI MS $(M+H)^+$; ^1H NMR (400 MHz, CD_3OD) δ 6.38 (s, 1H), 4.14 (m, 1H), 3.56 (m, 1H), 2.40 (s, 3H), 1.78-1.63 (m, 8H), 1.47 (s, 9H).

Step B: Synthesis of [*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-

cyclohexyl]- carbamic acid *tert*-butyl ester.

To a solution [*cis*-4-(6-chloro-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-carbamic acid *tert*-butyl ester (0.5 g, 0.0015 mol) in 2 mL 2-propanol were added dimethylamine (2.20 mL, 0.0044 mol) and DIEA (511 uL, 0.0029 mol). The mixture was heated in a microwave synthesizer at 160 °C for 2 hours. The reaction was repeated 17 more times (9 g total material) and the reaction mixtures were pooled. The solvent was evaporated and the material subjected to chromatography (2-4 % 2M NH_3 in MeOH / CH_2Cl_2) to yield [*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-carbamic acid *tert*-butyl ester (7.5 g, 0.021 mol, 81 %) as a white solid. ESI MS 350.4 $(M+H)^+$; ^1H NMR (400 MHz, CD_3OD) δ 5.35 (s, 1H), 3.72 (m, 1H), 3.54 (m, 1H), 3.05 (s, 6H), 2.30 (s, 3H), 1.75-1.61 (m, 8H), 1.47 (s, 9H).

Step C: Synthesis of *N*-(*cis*-4-amino-cyclohexyl)-2,*N*',*N*'-trimethyl-pyrimidine-4,6-diamine.

To a solution of [*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]- carbamic acid *tert*-butyl ester (7.5 g, 0.021 mol) in 50 mL CH_2Cl_2 was added TFA (3.3 mL, 0.043 mol). The solution was stirred at room temperature for 4 hours (or until the reaction was completed as judged by TLC). The excess solvent was evaporated off and the resulting oil was dissolved in 30 mL CH_2Cl_2. The organic layer was extracted with 30 mL of a dilute NaOH (aq) / $NaHCO_3$ (aq) solution (the aqueous layer was confirmed to remain basic during the extraction using pH paper indicator). The aqueous layer was back extracted twice with CH_2Cl_2 and the organic layers combined, dried over $MgSO_4$, and concentrated to yield *N*-(*cis*-4-amino-cyclohexyl)-2,*N*',*N*'-trimethyl-pyrimidine-4,6-diamine (5.3 g, 0.021 mol, 99%) as a white solid.
ESI MS 250.2 $(M+H)^+$; ^1H NMR (400 MHz, CD_3OD) δ 5.37 (s, 1H), 3.78 (m, 1H), 3.06 (s, 6H), 2.84 (m, 1H), 2.30 (s, 3H), 1.82-1.69 (m, 6H), 1.55-1.50 (m, 2H).

Step D: Synthesis of 5-bromo-furan-2-carboxylic acid [*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4- ylamino)-cyclohexyl]-amide trifluoroacetate.

To a solution of *N*-(*cis*-4-amino-cyclohexyl)-2,*N*',*N*'-trimethyl-pyrimidine-4,6-

diamine (30 mg, 0.12 mmol) in 0.5 mL DMF were added 5-bromo-2-furoic acid (23mg, 0.12 mmol), pyridine (14.6 uL, 0.18 mmol), and HATU (54.9 mg, 0.14 mmol). The reaction mixture was stirred overnight and then 0.5 mL DMSO was added to the mixture. The compound was then subject to purification by prep LCMS to yield 5-bromo-furan-2-carboxylic acid [*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4- ylamino)-cyclohexyl]-amide trifluoroacetate (25 mg, 0.047 mmol, 39 %) as a white solid TFA salt.

ESI MS 422.2 $(M+H)^+$; ^1H NMR (400 MHz, CD_3OD) δ 7.15 (d, 1H, $J = 3.6$ Hz), 6.64 (d, 1H, $J = 3.6$ Hz), 5.60 (s, 1H), 4.01 (m, 1H), 3.87 (m, 1H), 3.16 (s, 6H), 2.49 (s, 3H), 1.89-1.80 (m, 8H).

Example 49

5-Bromo-*N*-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-nicotinamide trifluoroacetate

Using the procedure of Step D of Example 48, the title compound was obtained (35 mg, 53 %) as a white solid.

ESI MS 433.0 $(M+H)^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.95 (d, 1H, $J = 1.6$ Hz), 8.84 (d, 1H, $J = 2.0$ Hz), 8.58 (m, 1H), 8.43 (t, 1H, $J = 2.0$ Hz), 5.60 (s, 1H), 4.05 (m, 1H), 3.88 (m, 1H), 3.22 (s, 6H), 2.49 (s, 3H), 1.93-1.84 (m, 8H).

Example 50

***N*-[*cis*-4-(6-Dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3,5-bis-trifluoromethyl-benzamide trifluoroacetate**

To a solution of *N*-(*cis*-4-amino-cyclohexyl)-2,*N*',*N*'-trimethyl-pyrimidine-4,6-diamine (30 mg, 0.12 mmol) in 0.5 mL DMF were added pyridine (14.6 uL, 0.18 mmol) and 3,5-bis(trifluoromethyl)benzoyl chloride (21.8 uL, 0.12 mmol). The reaction mixture was stirred overnight and then 0.5 mL of DMSO was added to the mixture. The compound was then subject to purification by prep LCMS to yield *N*-[*cis*-4-(6-dimethylamino-2-methyl- pyrimidin-4-ylamino)-cyclohexyl]-3,5-bis-trifluoromethyl-benzamide

trifluoroacetate (12 mg, 0.020 mmol, 17%) as a white solid TFA salt.

ESI MS 490.4 $(M+H)^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.46 (s, 2H), 8.19 (s, 1H), 5.42 (s, 1H), 4.06 (m, 1H), 3.86 (m, 1H), 3.09 (s, 6H), 2.34 (s, 3H), 1.93-1.79 (m, 9H).

Example 51

***N*-[*cis*-4-(6-Dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3,5-difluoro-benzamide trifluoroacetate**

Using the procedure of Step A of Example 50, the title compound was obtained (22 mg, 0.044 mmol, 36%) as a white solid.

ESI MS 390.2 $(M+H)^+$; ^1H NMR (400 MHz, CD_3OD) δ 7.50-7.46 (m, 2H), 7.22-7.16 (m, 1H), 5.60 (s, 1H), 4.02 (m, 1H), 3.87 (m, 1H), 3.22 (s, 6H), 2.49 (s, 3H), 1.90-1.81 (m, 8H).

Example 52

***N*-[*cis*-4-(3,5-Dimethoxy-benzylamino)-cyclohexyl]-2,*N'*,*N'*-trimethyl-pyrimidine-4,6-diamine bis-trifluoroacetate**

To a solution of *N*-(*cis*-4-amino-cyclohexyl)-2,*N'*,*N'*-trimethyl-pyrimidine-4,6-diamine (24.9 mg, 0.1 mmol) in 0.5 mL MeOH was added 3,5-dimethoxybenzaldehyde (16.6 mg, 0.1 mmol). The mixture was stirred at room temperature for a half an hour and then sodium triacetoxyborohydride (84.8 mg, 0.4 mmol) was added. The mixture was stirred at room temperature overnight and then 0.5 mL of DMSO was added to the mixture. The compound was then subject to purification by prep LCMS to yield *N*-[*cis*-4-(3,5-dimethoxy- benzylamino)-cyclohexyl]-2,*N'*,*N'*-trimethyl-pyrimidine-4,6-diamine bis-trifluoroacetate (27 mg, 0.043 mmol, 43%) as a white solid TFA salt.

ESI MS 400.5 $(M+H)^+$; ^1H NMR (400 MHz, CD_3OD) δ 6.72 (d, 2H, J = 2.0 Hz), 6.59 (t, 1H, J = 2.0 Hz), 5.59 (s, 1H), 4.22 (s, 2H), 3.97 (m, 1H), 3.84 (m, 1H), 3.79 (s, 6 H), 3.22 (s, 6H), 2.48 (s, 3H), 2.11-2.02 (m, 4H), 1.95-1.81 (m, 4H).

Example 53

***N*-[*cis*-4-(3-Bromo-benzylamino)-cyclohexyl]-2,*N'*,*N'*-trimethyl-pyrimidine-4,6-diamine bis-trifluoroacetate**

Using the procedure of Step A of Example 52, the title compound was obtained (35 mg, 0.054 mmol, 54%) as a white solid.

ESI MS 418.0 $(M+H)^+$; ^1H NMR (400 MHz, CD_3OD) δ 7.78 (s, 1H), 7.68 (d, 1H, J = 8.0 Hz), 7.55 (d, 1H, 7.6 Hz), 7.43 (t, 1H, J = 8.0 Hz), 5.60 (s, 1H), 4.29 (s, 2H), 3.21 (s, 6H), 2.48 (s, 3H), 2.12-2.03 (m, 4H), 1.95-1.85 (m, 4H).

Example 54

1-[*cis*-4-(6-Dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3-(3-methoxy-phenyl)-urea trifluoroacetate

To a solution of *N*-(*cis*-4-amino-cyclohexyl)-2,*N'*,*N'*-trimethyl-pyrimidine-4,6-diamine (24.9 mg, 0.1 mmol) in 0.5 mL DMSO was added 3-methoxyphenyl isocyanate (11.8 uL, 0.09 mmol). The mixture was stirred at room temperature overnight and then 0.5 mL of DMSO was added to the mixture. The compound was then subject to purification by prep LCMS to yield 1-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3- (3-methoxy- phenyl)-urea trifluoroacetate (19 mg, 0.037 mmol, 41%) as a white solid TFA salt.

ESI MS 399.2 $(M+H)^+$; ^1H NMR (400 MHz, CD_3OD) δ 7.15 (s, 1H), 7.14 (t, 1H, J = 2.4Hz), 6.86 (dd, 1H, J_1 = 8.0 Hz, J_2 = 2.0Hz), 6.57 (dd, 1H, J_1 = 8.0 Hz, J_2 = 2.4 Hz), 5.57 (s, 1H), 3.84 (m, 1H), 3.79 (s, 3H), 3.78 (m, 1H), 3.21 (s, 6H), 2.47 (s, 3H), 1.90-1.75 (m, 8H).

Example 55

1-(3,5-Difluoro-phenyl)-3-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-urea trifluoroacetate

Using the procedure of Step A of Example 54, the title compound was obtained

(22 mg, 0.043 mmol, 47%) as a white solid.

ESI MS 405.4 $(M+H)^+$; ^1H NMR (400 MHz, CD_3OD) δ 7.07-7.04 (m, 2H), 6.54-6.50 (m, 1H), 5.60 (s, 1H), 3.83 (m, 1H), 3.82 (m, 1H), 3.18 (s, 6H), 2.48 (s, 3H), 1.90-1.83 (m, 4H), 1.79-1.75 (m, 4H).

Example 56

***N*-[*cis*-4-(6-Dimethylamino-2-methylsulfanyl-pyrimidin-4-ylamino)-cyclohexyl]-3,4-difluoro-benzamide trifluoroacetate**

Step A: Synthesis of *cis*-[4-(3,4-difluoro-benzoylamino)-cyclohexyl]-carbamic acid tert-butyl ester.

To a solution of *cis*-(4-amino-cyclohexyl)-carbamic acid *tert*-butyl ester (3 g, 0.014 mol) in CH_2Cl_2 (50 mL) was added DIEA (3.6 mL, 0.021 mol). The mixture was cooled on an ice bath and 3,4-difluorobenzoyl chloride (1.9 mL, 0.015 mol) was slowly added. The mixture was brought to room temperature and stirred for 1 hour. The solvent was then concentrated and the resulting oil subjected to chromatography (0-70 % ethyl acetate in hexanes). Upon evaporation of solvents, a precipitate crashed out which was filtered and washed with 70% cold ether in hexanes to yield *cis*-[4-(3,4-difluoro-benzoylamino)-cyclohexyl]-carbamic acid tert-butyl ester (4.4 g, 0.012 mol, 89%) as a white solid.

ESI 355.4 $M+H^+$; ^1H NMR (400 MHz, CD_3OD) δ 7.78-7.72 (m, 1H), 7.68-7.64 (m, 1H), 7.39-7.33 (m, 1H), 3.93 (m, 1H), 3.61 (m, 1H), 1.78-1.68 (m, 8H), 1.45 (s, 9H).

Step B: Synthesis of *cis*-*N*-(4-amino-cyclohexyl)-3,4-difluoro-benzamide.

To a solution of *cis*-[4-(3,4-difluoro-benzoylamino)-cyclohexyl]-carbamic acid tert-butyl ester (4.4 g, 0.012 mol) in CH_2Cl_2 (50 mL) was added TFA (1.9 mL, 0.025 mol). The solution was stirred at room temperature for 4 hours (or until the reaction was complete as judged by TLC). The excess solvent was evaporated off and the resulting oil was dissolved in 30 mL CH_2Cl_2. The organic layer was extracted with 30 mL of a dilute NaOH (aq) / $NaHCO_3$ (aq) solution (the aqueous layer was confirmed to remain basic

during the extraction using pH paper indicator). The aqueous layer was back extracted twice with CH_2Cl_2 and the organic layers combined, dried over $MgSO_4$, and concentrated to yield *cis-N*-(4-amino-cyclohexyl)-3,4-difluoro-benzamide (2.9 g, 0.011 mol, 90%) as a white solid.

ESI 255.4 $M+H^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.17 (d, 1H, J = 4.8 Hz), 7.93-7.88 (m, 1H), 7.80-7.70 (m, 4H), 7.58-7.51 (m, 1H), 3.86 (m, 1H), 3.12 (m, 1H), 1.91-1.87 (m, 2H), 1.73-1.60 (m, 6H).

Step C: Synthesis of *cis-N*-[4-(6-chloro-2-methylsulfanyl-pyrimidin-4-ylamino)-cyclohexyl]-3,4-difluoro-benzamide.

To a solution of 4,6-dichloro-2-(methylthio)-pyrimidine (19.5 mg, 0.1 mmol) in IPA (0.6 mL) were added DIEA (35 uL, 0.2 mmol) and *cis-N*-(4-amino-cyclohexyl)-3,4-difluoro-benzamide (25.4 mg, 0.1 mmol). The mixture was then heated in a microwave at 170 °C for 30 minutes. The reaction mixture was cooled and concentrated and the resulting oil was purified by column (0-100% ethyl acetate in hexanes) to yield *cis-N*-[4-(6-chloro-2-methylsulfanyl-pyrimidin-4-ylamino)-cyclohexyl]-3,4-difluoro-benzamide (37 mg, 0.090 mmol, 90%) as a colorless oil.

ESI MS 413.2 $(M+H)^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.23 (m, 1H), 7.81-7.76 (m, 1H), 7.72-7.68 (m, 1H), 7.43-7.36 (m, 1H), 6.27 (s, 1H), 4.17 (m, 1H), 4.00 (m, 1H), 2.51 (s, 3H), 1.94-1.79 (m, 8H).

Step D: Synthesis of *N*-[*cis*-4-(6-dimethylamino-2-methylsulfanyl-pyrimidin-4-ylamino)-cyclohexyl]-3,4-difluoro-benzamide trifluoroacetate.

To a solution of *cis-N*-[4-(6-chloro-2-methylsulfanyl-pyrimidin-4-ylamino)-cyclohexyl]-3,4-difluoro-benzamide (73 mg, 0.18 mmol) in IPA (0.8 mL) were added DIEA (62 uL, 0.35 mmol) and dimethylamine (265 uL, 0.53 mmol). The mixture was then heated in a microwave at 170 °C for 1 hour. The reaction mixture was cooled and concentrated and the resulting oil was re-dissolved into 1 mL DMSO and purified by prep LCMS to yield *N*-[*cis*-4-(6-dimethylamino-2-methylsulfanyl-pyrimidin-4-ylamino)-cyclohexyl]-3,4-difluoro-benzamide trifluoroacetate (18.4 mg, 0.034 mmol, 19%) as a

TFA salt.

ESI MS 422.2 $(M+H)^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.28 (m, 1H), 7.82-7.76 (m, 1H), 7.73-7.69 (m, 1H), 7.43-7.36 (m, 1H), 4.88 (s, 1H), 4.02 (m, 1H), 3.89 (m, 1H), 3.11 (s, 6H), 2.66 (s, 3H), 1.92-1.79 (m, 8H).

Example 57

***N*-[*cis*-4-(6-Dimethylamino-pyrimidin-4-ylamino)-cyclohexyl]-3,4-difluoro-benzamide trifluoroacetate**

To a solution of 4,6-dichloropyrimidine (14.9 mg, 0.1 mmol) in IPA (1 mL) were added DIEA (35 uL, 0.2 mmol) and *cis*-*N*-(4-amino-cyclohexyl)-3,4-difluoro-benzamide from Step B Example 56 (25.4 mg, 0.1 mmol). The mixture was then heated in a microwave at 170 °C for 15 minutes. The reaction mixture was cooled and then DIEA (35 uL, 0.2 mmol) and dimethylamine (150 uL, 0.3 mmol) were added. The mixture was then heated in a microwave at 170 °C for 1 hour. The reaction mixture was cooled and concentrated and the resulting oil was re-dissolved into 1 mL DMSO and purified by prep LCMS to yield *N*-[*cis*-4-(6-dimethylamino-pyrimidin-4-ylamino)-cyclohexyl]-3,4-difluoro-benzamide trifluoroacetate (11.7 mg, 0.024 mmol, 24%) as a TFA salt.

ESI MS 376.3 $(M+H)^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.27 (m, 1H), 8.18 (s, 1H), 7.82-7.76 (m, 1H), 7.73-7.69 (m, 1H), 7.43-7.36 (m, 1H), 5.71 (s, 1H), 4.02 (m, 1H), 3.88 (m, 1H), 3.23 (s, 6H), 1.90-1.84 (m, 8H).

Example 58

***N*-[*cis*-4-(6-Dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3,4-difluoro-benzamide trifluoroacetate**

To a solution of 2-methyl-4,6-dichloropyrimidine (32.6 mg, 0.2 mmol) in IPA (1 mL) were added DIEA (70 uL, 0.4 mmol) and *cis*-*N*-(4-amino-cyclohexyl)-3,4-difluoro-benzamide from Step B Example 56 (50.8 mg, 0.2 mmol). The mixture was then heated in

a microwave at 170 °C for 15 minutes. The reaction mixture was cooled and then DIEA (70 uL, 0.4 mmol) and dimethylamine (300 uL, 0.3 mmol) were added. The mixture was then heated in a microwave at 170 °C for 1 hour. The reaction mixture was cooled and concentrated and the resulting oil was re-dissolved into 1 mL DMSO and purified by prep LCMS to yield *N*-[*cis*-4-(6-dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3,4-difluoro-benzamide trifluoroacetate (32.2 mg, 0.064 mmol, 64%) as a TFA salt. ESI MS 390.2 $(M+H)^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 8.20 (s, 1H), 8.17 (m, 1H), 7.81-7.78 (m, 1H), 7.72-7.71 (m, 1H), 7.42-7.40 (m, 1H), 4.10 (m, 1H), 4.09 (m, 1H), 3.16 (s, 6H), 2.16 (s, 3H), 2.02-1.82 (m, 8H).

Example 59

3,4-Dichloro-*N*-[*cis*-4-(2-dimethylamino-6-methyl-pyrimidin-4-ylamino)-cyclohexyl]-benzamide trifluoroacetate

Step A: Synthesis of *cis*-[4-(2-chloro-6-methyl-pyrimidin-4-ylamino)-cyclohexyl]-carbamic acid tert-butyl ester.

To a solution of 2,4-dichloro-6-methylpyrimidine (3.7 g, 0.023 mol) in 30 mL methanol were added DIEA (5.89 mL, 0.034 mmol) and *cis*-(4-amino-cyclohexyl)-carbamic acid *tert*-butyl ester (5.3 g, 0.025 mol). The mixture was refluxed overnight, cooled, and concentrated. The resulting oil was subjected to chromatography (0-100% ethyl acetate in hexanes) to yield *cis*-[4-(2-chloro-6-methyl-pyrimidin-4-ylamino)-cyclohexyl]-carbamic acid tert-butyl ester (5.1 g, 0.015 mol, 66%) as a white solid. ESI MS 341.4 $(M+H)^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 6.31 (s, 1H), 4.12 (m, 1H), 3.56 (m, 1H), 2.26 (s, 3H), 1.78-1.67 (m, 8H), 1.48 (s, 9H).

Step B: Synthesis of *cis*-[4-(2-dimethylamino-6-methyl-pyrimidin-4-ylamino)-cyclohexyl]-carbamic acid tert-butyl ester.

To a solution *cis*-[4-(2-chloro-6-methyl-pyrimidin-4-ylamino)-cyclohexyl]-carbamic acid tert-butyl ester (0.5 g, 0.0015 mol) in 2 mL 2-propanol were added dimethylamine (1.47 mL, 0.0029 mol) and DIEA (511 uL, 0.0029 mol). The mixture was

heated in a microwave synthesizer at 170 °C for 1 hour. The reaction was repeated 9 more times (5 g total material) and the reaction mixtures were pooled. The solvent was evaporated and the material subjected to chromatography (2-4 % 2M NH_3 in MeOH / CH_2Cl_2) to yield *cis*-[4-(2-dimethylamino-6-methyl-pyrimidin-4-ylamino)-cyclohexyl]-carbamic acid tert-butyl ester (2.2 g, 0.0063 mol, 43 %) as a white solid.

ESI MS 350.2 $(M+H)^+$; ^1H NMR (400 MHz, CD_3OD) δ 5.68 (s, 1H), 3.95 (m, 1H), 3.54 (m, 1H), 3.11 (s, 6H), 2.16 (s, 3H), 1.77-1.64 (m, 8H), 1.47 (s, 9H).

Step C: Synthesis of *cis*-4-(2-dimethylamino-6-methyl-pyrimidin-4-ylamino)-1-amino-cyclohexane.

To a solution of *cis*-[4-(2-dimethylamino-6-methyl-pyrimidin-4-ylamino)-cyclohexyl]-carbamic acid tert-butyl ester (2.2 g, 0.0063 mol) in 15 mL CH_2Cl_2 was added TFA (0.97 mL, 0.013 mol). The solution was stirred at room temperature for 4 hours (or until the reaction was complete as judged by TLC). The excess solvent was evaporated off and the resulting oil was dissolved in 30 mL CH_2Cl_2. The organic layer was extracted with 30 mL of a dilute NaOH (aq) / $NaHCO_3$ (aq) solution (the aqueous layer was confirmed to remain basic during the extraction using pH paper indicator). The aqueous layer was back extracted twice with CH_2Cl_2 and the organic layers combined, dried over $MgSO_4$, and concentrated to yield *cis*-4-(2-dimethylamino-6-methyl-pyrimidin-4-ylamino)-1-amino-cyclohexane (1.3 g, 0.0052 mol, 83%) as a white solid.

ESI MS 250.2 $(M+H)^+$; ^1H NMR (400 MHz, CD_3OD) δ 5.70 (s, 1H), 4.00 (m, 1H), 3.11 (s, 6H), 2.84 (m, 1H), 2.16 (s, 3H), 1.86-1.80 (m, 2H), 1.76-1.66 (m, 4H), 1.57-1.49 (m, 2H).

Step D: Synthesis of 3,4-dichloro-*N*-[*cis*-4-(2-dimethylamino-6-methyl-pyrimidin-4-ylamino)-cyclohexyl]-benzamide trifluoroacetate.

To a solution of *cis*-4-(2-dimethylamino-6-methyl-pyrimidin-4-ylamino)-1-amino-cyclohexane (20 mg, 0.080 mmol) in 0.5 mL DMF was added pyridine (9.7 uL, 0.12 mmol) and 3,4-dichlorobenzoyl chloride (11.1 uL, 0.076 mmol). The reaction mixture was stirred overnight and then 0.5 mL of DMSO was added to the mixture. The compound was then subject to purification by prep LCMS to yield 3,4-dichloro-*N*-[*cis*-4-(2-

dimethylamino-6- methyl-pyrimidin-4-ylamino)-cyclohexyl]-benzamide trifluoroacetate (10 mg, 0.019 mmol, 24%) as a TFA salt.

ESI MS 422.2 $(M+H)^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.00 (d, 1H, J = 2.0 Hz), 7.76 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz), 7.65 (d, 1H, J = 8.4 Hz), 6.01 (s, 1H), 4.23 (m, 1H), 4.00 (m, 1H), 3.26 (s, 6H), 2.34 (s, 3H), 1.98-1.81 (m, 8H).

Example 60

4-Cyano-*N*-[*cis*-4-(2-dimethylamino-6-methyl-pyrimidin-4-ylamino)-cyclohexyl]-benzamide trifluoroacetate

Using the procedure of Step D of Example 59, the title compound was obtained (11 mg, 0.022 mmol, 29%).

ESI MS 379.2 $(M+H)^+$; ^1H NMR (400 MHz, CD_3OD) δ 7.97 (d, 2H, J = 8.0 Hz), 7.86 (d, 2H, J = 8.4 Hz), 6.01 (s, 1H), 4.23 (m, 1H), 4.03 (m, 1H), 3.26 (s, 6H), 2.34 (s, 3H), 1.99-1.82 (m, 8H).

Example 61

***N*-[*cis*-4-(2-Dimethylamino-6-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3,4-diethoxy-benzamide trifluoroacetate**

To a solution of *cis*-4-(2-dimethylamino-6-methyl-pyrimidin-4-ylamino)-1-amino-cyclohexane (20 mg, 0.080 mmol) in 0.5 mL DMF were added 3,4-diethoxy-benzoic acid (16.0 mg, 0.076 mmol), pyridine (9.7 uL, 0.12 mmol), and HATU (36.6 mg, 0.096 mmol). The reaction mixture was stirred overnight and then 0.5 mL DMSO was added to the mixture. The compound was then subject to purification by prep LCMS to yield *N*-[*cis*-4-(2-dimethylamino-6-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3,4-diethoxy- benzamide trifluoroacetate (11 mg, 0.020 mmol, 26%) as a TFA salt.

ESI MS 442.4 $(M+H)^+$; ^1H NMR (400 MHz, CD_3OD) δ 7.47-7.44 (m, 2H), 7.02-7.00 (m, 1H), 6.01 (s, 1H), 4.23 (m, 1H), 4.15 (q, 4H, J = 7.0 Hz), 4.00 (m, 1H), 3.26 (s, 3H), 2.34 (s, 3H), 1.99-1.81 (m, 8H), 1.45 (t, 6H, J = 7.2 Hz).

Example 62

3-Chloro-*N*-[*cis*-4-(2-dimethylamino-6-methyl-pyrimidin-4-ylamino)-cyclohexyl]-5-fluoro-benzamide trifluoroacetate

Using the procedure of Step A of Example 61, the title compound was obtained (12 mg, 0.023 mmol, 30%).

ESI MS 406.4 $(M+H)^+$; ^1H NMR (400 MHz, CD_3OD) δ 7.71 (s, 1H), 7.57-7.53 (m, 1H), 7.45-7.42 (m, 1H), 6.00 (s, 1H), 4.23 (m, 1H), 4.00 (m, 1H), 3.26 (s, 6H), 2.34 (s, 3H), 1.99-1.82 (m, 8H).

Example 63

***N*-[*cis*-4-(2-Dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3,5-dimethoxy-benzamide trifluoroacetate**

Step A: Synthesis of *cis*-[4-(2-chloro-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-carbamic acid tert-butyl ester.

To a solution of 2,4-dichloro-5-methylpyrimidine (1.0 g, 6.13 mmol) in 2 mL 2-propanol were added DIEA (1.6 mL, 9.20 mmol) and *cis*-(4-amino-cyclohexyl)-carbamic acid *tert*-butyl ester (1.45 g, 6.75 mmol). The mixture was heated in a microwave synthesizer at 150 °C for 15 minutes. The solvent was evaporated and the material subjected to chromatography (0-70% ethyl acetate in hexanes) to yield *cis*-[4-(2-chloro-5-methyl- pyrimidin-4-ylamino)-cyclohexyl]-carbamic acid tert-butyl ester (1.7 g, 4.86 mmol, 79%) as a white solid.

ESI MS 341.2 $(M+H)^+$; ^1H NMR (400 MHz, CD_3OD) δ 7.76 (s, 1H), 4.12 (m, 1H), 3.67 (m, 1H), 2.05 (s, 3H), 1.82-1.70 (m, 8H), 1.48 (s, 9H).

Step B: Synthesis of *cis*-[4-(2-dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-carbamic acid tert-butyl ester.

To a solution *cis*-[4-(2-chloro-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-carbamic acid tert-butyl ester (0.5 g, 0.0015 mol) in 2 mL 2-propanol were added dimethylamine (1.47 mL, 0.0029 mol) and DIEA (511 uL, 0.0029 mol). The mixture was

heated in a microwave synthesizer at 170 °C for 1 hour. The reaction was repeated 2 more times (1.5 g total material) and the reaction mixtures were pooled. The solvent was evaporated and the material subjected to chromatography (2-4 % 2M NH_3 in MeOH / CH_2Cl_2) to yield *cis*-[4-(2-dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-carbamic acid tert-butyl ester (1.3 g, 0.0037 mol, 85 %) as a white solid. ESI MS 350.2 $(M+H)^+$; ^1H NMR (400 MHz, CD_3OD) δ 7.53 (s, 1H), 4.13 (m, 1H), 3.63 (m, 1H), 3.09 (s, 6H), 1.94 (s, 3H), 1.83-1.70 (m, 8H), 1.48 (s, 9H).

Step C: Synthesis of *cis*-4-(2-dimethylamino-5-methyl-pyrimidin-4-ylamino)-1-amino-cyclohexane.

To a solution of *cis*-[4-(2-dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-carbamic acid tert-butyl ester (1.3 g, 0.0037 mol) in 10 mL CH_2Cl_2 was added TFA (0.57 mL, 0.0074 mol). The solution was stirred at room temperature for 4 hours (or until the reaction was complete as judged by TLC). The excess solvent was evaporated off and the resulting oil was dissolved in 30 mL CH_2Cl_2. The organic layer was extracted with 30 mL of a dilute NaOH (aq) / $NaHCO_3$ (aq) solution (the aqueous layer was confirmed to remain basic during the extraction using pH paper indicator). The aqueous layer was back extracted twice with CH_2Cl_2 and the organic layers combined, dried over $MgSO_4$, and concentrated to yield *cis*-4-(2-dimethylamino-5-methyl-pyrimidin-4-ylamino)-1-amino-cyclohexane (0.88 g, 0.0035 mol, 95%) as a white solid.

ESI MS 250.2 $(M+H)^+$; ^1H NMR (400 MHz, CD_3OD) δ 7.53 (s, 1H), 4.17 (m, 1H), 3.09 (s, 6H), 2.94 (m, 1H), 1.96 (s, 3H), 1.86-1.71 (m, 6H), 1.62-1.59 (m, 2H).

Step D: Synthesis of *N*-[*cis*-4-(2-dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3,5-dimethoxy-benzamide trifluoroacetate.

To a solution of *cis*-4-(2-dimethylamino-5-methyl-pyrimidin-4-ylamino)-1-amino-cyclohexane (20 mg, 0.080 mmol) in 0.5 mL DMF were added pyridine (9.7 uL, 0.12 mmol) and 3,5-dimethoxybenzoyl chloride (15.3 mg, 0.076 mmol). The reaction mixture was stirred overnight and then 0.5 mL of DMSO was added to the mixture. The compound was then subject to purification by prep LCMS to yield *N*-[*cis*-4-(2-dimethylamino-5-

methyl- pyrimidin-4-ylamino)-cyclohexyl]-3,5-dimethoxy-benzamide trifluoroacetate (14 mg, 0.027 mmol, 35%) as a TFA salt.

ESI MS 414.4 $(M+H)^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.00 (s, 1H), 7.48 (s, 1H), 7.19 (d, 1H, J = 2.4 Hz), 6.69 (t, 1H, J = 2.4 Hz), 4.31 (m, 1H), 4.10 (m, 1H), 3.85 (s, 6H), 3.23 (s, 6H), 2.32 (s, 3H), 2.10-1.82 (m, 8H).

Example 64

3,4-Dichloro-*N*-[*cis*-4-(2-dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-benzamide trifluoroacetate

Using the procedure of Step D of Example 63, the title compound was obtained (15 mg, 0.028 mmol, 37%).

ESI MS 422.2 $(M+H)^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.24 (m, 1H), 8.02 (d, 1H, J = 2.0 Hz), 7.78 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2.0 Hz), 7.67 (d, 1H, J = 8.4 Hz), 7.48 (s, 1H), 4.31 (m, 1H), 4.10 (m, 1H), 3.23 (s, 6H), 2.10 (s, 3H), 2.00-1.82 (m, 8H).

Example 65

***N*-[*cis*-4-(2-Dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3,4-diethoxy-benzamide trifluoroacetate**

To a solution of *cis*-4-(2-dimethylamino-5-methyl-pyrimidin-4-ylamino)-1-amino-cyclohexane (20 mg, 0.080 mmol) in 0.5 mL DMF were added 3,4-diethoxy-benzoic acid (16.0 mg, 0.076 mmol), pyridine (9.7 uL, 0.12 mmol), and HATU (36.6 mg, 0.096 mmol). The reaction mixture was stirred overnight and then 0.5 mL DMSO was added to the mixture. The compound was then subject to purification by prep LCMS to yield *N*-[*cis*-4-(2-dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3,4-diethoxy- benzamide trifluoroacetate (12 mg, 0.022 mmol, 28%) as a TFA salt.

ESI MS 442.4 $(M+H)^+$; ^1H NMR (400 MHz, CD_3OD) δ 7.49-7.46 (m, 3H), 7.02 (d, 1H, J = 8.0 Hz), 4.31 (m, 1H), 4.16 (q, 4H, J = 7.0 Hz), 4.10 (m, 1 H), 3.23 (s, 6H), 2.10 (s, 3H), 2.01-1.81 (m, 8H), 1.46 (t, 6H, J = 7.0 Hz).

Example 66

3-Chloro-*N*-[*cis*-4-(2-dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-5-fluoro-benzamide trifluoroacetate

Using the procedure of Step A of Example 65, the title compound was obtained (12 mg, 0.023 mmol, 30%).

ESI MS 406.2 $(M+H)^+$; ^1H NMR (400 MHz, CD_3OD) δ 7.73 (s, 1H), 7.59-7.56 (m, 1H), 7.48 (s, 1H), 7.46-7.43 (m, 1H), 4.31 (m, 1H), 4.10 (m, 1H), 3.23 (s, 6H), 2.10 (s, 3H), 2.03-1.81 (m, 8H).

Example 67

***N*-[*cis*-4-(6-Dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-3,5-bis-trifluoromethyl-benzamide trifluoroacetate**

Step A: Synthesis of *cis*-(4-amino-cyclohexylmethyl)-carbamic acid benzyl ester.

To a solution of *cis*-(4-aminomethyl-cyclohexyl)-carbamic acid tert-butyl ester (25 g, 0.11 mol) in CH_2Cl_2 (300 mL) was added DIEA (22.9 mL, 0.13 mol). The mixture was cooled on an ice bath and benzyl chloroformate (17.3 mL, 0.12 mol) was slowly added. The mixture was removed from the ice bath and stirred overnight. The solvent was removed in vacuo and the resulting oil dissolved in MeOH (250 mL). Concentrated HCl (75 mL) was slowly added to the mixture with stirring. The reaction was allowed to stir for 4 more hours and then the solvent was removed in vacuo resulting in a precipitate. A copious amount of water (2 L) was added to dissolve the resulting HCl salt precipitate, which was then made basic with slow addition of a concentrated NaOH solution. The aqueous layer was extracted 3 times with ethyl acetate (1 L). The organic layers were combined, dried over $MgSO_4$, and concentrated to yield *cis*-(4-amino-cyclohexylmethyl)-carbamic acid benzyl ester (24.5 g, 0.093 mol, 85%) as an oil.

ESI MS m/e 263.2 $(M+H)^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 7.36-7.25 (m, 5H), 4.99 (s, 2H), 2.90 (t, J = 6.4 Hz, 2H), 2.81 (m, 1H), 143-1.34 (m, 8H).

Step B: Synthesis of *cis*-[4-(6-chloro-2-methyl-pyrimidin-4-ylamino)-

cyclohexylmethyl]-carbamic acid benzyl ester.

To a solution of 4,6-dichloro-2-methyl-pyrimidine (1.0 g, 6.1 mmol) in 2 mL 2-propanol were added DIEA (1.6 mL, 9.2 mmol) and *cis*-(4-amino-cyclohexylmethyl)-carbamic acid benzyl ester (1.8 g, 6.7 mmol). The mixture was heated in a microwave synthesizer at 160 °C for 20 minutes. The reaction was repeated 2 more times (3 g total material) and the reaction mixtures were pooled. The solvent was evaporated and the material subjected to chromatography (0-100% ethyl acetate in hexanes) to yield *cis*-[4-(6-chloro-2-methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-carbamic acid benzyl ester (6.5 g, 0.017 mol, 91 %) as a white solid.

ESI MS m/e 389.2 $(M+H)^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.26 (m, 5H), 6.17 (s, 1H), 5.09 (s, 2H), 4.89 (m, 1H), 3.10 (t, J = 6.0 Hz, 2H), 2.46 (s, 3H), 1.80-1.67 (m, 2H), 1.66-1.60 (m, 4H), 1.30-1.22 (m, 2H).

Step C: Synthesis of *cis*-[4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-carbamic acid benzyl ester.

To a solution of *cis*-[4-(6-chloro-2-methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-carbamic acid benzyl ester (0.5 g, 1.3 mmol) in 2 mL 2-propanol were added DIEA (224 uL, 1.3 mmol) and dimethylamine (1.3 mL, 2.6 mmol). The mixture was heated in a microwave synthesizer at 170 °C for 30 minutes. The reaction was repeated 7 more times (8g total material) and the reaction mixtures pooled. The solvent was evaporated and the material subjected to chromatography (0-100% ethyl acetate in hexanes to remove starting material, followed by <5% MeOH in CH_2Cl_2) to yield *cis*-[4-(6-dimethylamino-2- methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-carbamic acid benzyl ester (3.8 g, 9.6 mmol, 94%) as a white solid.

ESI MS m/e 398.2 $(M+H)^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.6-7.26 (m, 5H), 5.10 (s, 1H), 5.09 (s, 2H), 5.06 (m, 1H), 3.69 (m, 1H), 3.09 (m, 8H), 2.40 (s, 3H), 1.87-1.83 (m, 2H), 1.65-1.56 (m, 4H), 1.42-1.36 (m, 2H).

Step D: Synthesis of *cis*-*N*-(4-aminomethyl-cyclohexyl)-2,*N'*,*N'*-trimethyl-pyrimidine-4,6-diamine.

To a solution of *cis*-[4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-carbamic acid benzyl ester (3.8 g, 9.6 mmol) in EtOH (100 mL) was added 10% Pd/C (380 mg). The reaction mixture was stirred at room temperature under an H_2(g) atmosphere for 15 hours. The H_2(g) atmosphere was removed and the mixture washed through a plug of celite with ethyl acetate. The solvent was concentrated and the material was subjected to chromatography (2-4 % 2M NH_3 in MeOH / CH_2Cl_2) to yield *cis*-*N*-(4-aminomethyl-cyclohexyl)-2,*N*',*N*'-trimethyl-pyrimidine-4,6-diamine (1.7 g, 6.5 mmol, 64%) as a white solid.

ESI MS m/e 264.2 $(M+H)^+$; ^{1}H NMR (400 MHz, DMSO) δ 6.29 (m,1H), 5.33 (s, 1H), 3.87 (m, 1H), 2.91 (s, 6H), 2.42 (s, 2H), 2.15 (s, 3H), 1.55-1.29 (m, 8H).

Step E: Synthesis of *N*-[*cis*-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-3,5-bis-trifluoromethyl-benzamide trifluoroacetate

To a solution of *cis*-*N*-(4-aminomethyl-cyclohexyl)-2,*N*',*N*'-trimethyl-pyrimidine-4,6-diamine (26 mg, 0.10 mmol) in 0.5 mL DMF were added pyridine (12.1 uL, 0.15 mmol) and 3,5-bis(trifluoromethyl)benzoyl chloride (18.1 uL, 0.10 mmol). The reaction mixture was stirred overnight and then 0.5 mL of DMSO was added to the mixture. The compound was then subject to purification by prep LCMS to yield *N*-[*cis*-4-(6-dimethylamino-2– methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-3,5-bis-trifluoromethyl-benzamide trifluoroacetate (11.9 mg, 0.019 mmol, 19%) as a white solid TFA salt.

ESI MS m/e 504.2 $(M+H)^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 9.03 (m, 1H), 8.47 (s, 2H), 8.20 (s, 1H), 5.58 (s, 1H), 3.88 (s, 1H), 3.43 (t, J = 6.4 Hz, 2H), 3.20 (s, 6H), 2.48 (s, 3H), 1.90-1.75 (m, 6H), 1.54-1.46 (m, 2H).

Example 68

***N*-[*cis*-4-(6-Dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-4-trifluoromethoxy-benzamide trifluoroacetate**

Using the procedure of Step E of Example 67, the title compound was obtained

(18.7 mg, 0.033 mmol, 33%) as a white solid.

ESI MS m/e 452.2 $(M+H)^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.65 (m, 1H), 7.96 (d, J = 9.4 Hz, 2H), 7.40 (d, J = 8.4 Hz), 5.58 (s, 1H), 3.87 (s, 1H), 3.39 (t, J = 6.4 Hz), 3.19 (s, 6H), 2.48 (s, 3H), 1.88-1.75 (m, 6H), 1.53-1.44 (m, 2H).

Examples 69-72

Compounds 69 to 72 were prepared in a similar manner as described in Example 48 using the appropriate carboxylic acid and amine intermediate of Step D.

Examples 73-107

Compounds 73 to 107 were prepared in a similar manner as described in Example 50 using the appropriate acid chloride and amine intermediate of Step A.

Examples 108-110

Compounds 108 to 110 were prepared in a similar manner as described in Example 52 using the appropriate aldehyde and amine intermediate of Step A.

Examples 111-113

Compounds 111 to 113 were prepared in a similar manner as described in Example 54 using the appropriate isocyanate and amine intermediate of Step A.

Examples 114-117

Compounds 114 to 117 were prepared in a similar manner as described in Example 48 using the appropriate carboxylic acid and amine intermediate of Step D.

Examples 118-125

Compounds 118 to 125 were prepared in a similar manner as described in Example 63 using the appropriate acid chloride and amine intermediate of Step D.

Examples 126-133

Compounds 126 to 133 were prepared in a similar manner as described in Example 65 using the appropriate carboxylic acid and amine intermediate of Step A.

Examples 134-140

Compounds 134 to 140 were prepared in a similar manner as described in Example 59 using the appropriate acid chloride and amine intermediate of Step D.

Examples 141-148

Compounds 141 to 148 were prepared in a similar manner as described in Example 61 using the appropriate carboxylic acid and amine intermediate of Step A.

Examples 149-167

Compounds 149 to 167 were prepared in a similar manner as described in Example 67 using the appropriate acid chloride and amine intermediate of Step E.

Ex. No.	compound name	MS
69	N-[cis-4-(6-Dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3,4-diethoxy-benzamide	442.4 (M+H)
70	N-[cis-4-(6-Dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3-ethoxy-benzamide	398.2 (M+H)
71	N-[cis-4-(6-Dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3,5-diethoxy-benzamide	442.2 (M+H)
72	N-[cis-4-(6-Dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3-isopropoxy-benzamide	412.4 (M+H)
73	3-Bromo-N-[cis-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-4-fluoro-benzamide	450.2 (M+H)
74	4-Difluoromethoxy-N-[cis-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-benzamide	420.2 (M+H)
75	4-Chloro-N-[cis-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3-methyl-benzamide	402 (M+H)
76	3-Chloro-N-[cis-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-5-fluoro-benzamide	406.2 (M+H)
77	3-Difluoromethoxy-N-[cis-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-benzamide	420.2 (M+H)
78	3-Chloro-N-[cis-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-4-methyl-benzamide	402.2 (M+H)
79	4-Bromo-N-[cis-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-benzamide	432.2 (M+H)
80	N-[cis-4-(6-Dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3,5-dimethoxy-benzamide	414.6 (M+H)
81	3,4-Dichloro-N-[cis-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-benzamide	422.2 (M+H)
82	4-Cyano-N-[cis-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-benzamide	379.2 (M+H)
83	N-[cis-4-(6-Dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-4-methoxy-benzamide	384.2 (M+H)
84	3-Cyano-N-[cis-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-benzamide	379.2 (M+H)
85	3,5-Dichloro-N-[cis-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-benzamide	422.2 (M+H)
86	N-[cis-4-(6-Dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3-methoxy-benzamide	384.2 (M+H)
87	N-[cis-4-(6-Dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-4-fluoro-3-methyl-benzamide	386.2 (M+H)
88	N-[cis-4-(6-Dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3-fluoro-5-trifluoromethyl-benzamide	440.4 (M+H)
89	N-[cis-4-(6-Dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-4-fluoro-benzamide	372.2 (M+H)

Ex. No.	compound name	MS
90	4-Bromo-N-[cis-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3-methyl-benzamide	446.2 (M+H)
91	N-[cis-4-(6-Dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3-fluoro-4-methyl-benzamide	386.2 (M+H)
92	4-Chloro-N-[cis-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-benzamide	388.4 (M+H)
93	N-[cis-4-(6-Dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3-fluoro-benzamide	372.2 (M+H)
94	N-[cis-4-(6-Dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3-trifluoromethoxy-benzamide	438.4 (M+H)
95	N-[cis-4-(6-Dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3-ethyl-benzamide	382.4 (M+H)
96	3-Bromo-N-[cis-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-benzamide	432.3 (M+H)
97	N-[cis-4-(6-Dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3-trifluoromethyl-benzamide	422.1 (M+H)
98	N-[cis-4-(6-Dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3-fluoro-4-trifluoromethyl-benzamide	440.6 (M+H)
99	3-Chloro-N-[cis-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-benzamide	388.5 (M+H)
100	N-[cis-4-(6-Dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-4-fluoro-3-trifluoromethyl-benzamide	440.6 (M+H)
101	N-[cis-4-(6-Dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3,4-difluoro-benzamide	390.2 (M+H)
102	3-Chloro-N-[cis-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-4-fluoro-benzamide	406.3 (M+H)
103	N-[cis-4-(6-Dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-4-trifluoromethoxy-benzamide	438.1 (M+H)
104	N-[cis-4-(6-Dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-4-methyl-benzamide	368.3 (M+H)
105	N-[cis-4-(6-Dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3-methyl-benzamide	368.2 (M+H)
106	N-[cis-4-(6-Dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-4-trifluoromethyl-benzamide	422.3 (M+H)
107	2,2-Difluoro-benzo[1,3]dioxole-5-carboxylic acid [cis-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-amide	434.1 (M+H)
108	N-{cis-4-[(1H-Indol-2-ylmethyl)-amino]-cyclohexyl}-2,N',N'-trimethyl-pyrimidine-4,6-diamine	379.4 (M+H)
109	2,N,N-Trimethyl-N'-[cis-4-(3-trifluoromethoxy-benzylamino)-cyclohexyl]-pyrimidine-4,6-diamine	424.2 (M+H)
110	N-[cis-4-(3,4-Difluoro-benzylamino)-cyclohexyl]-2,N',N'-trimethyl-pyrimidine-4,6-diamine	376.6 (M+H)

Ex. No.	compound name	MS
111	1-(3,4-Dimethoxy-phenyl)-3-[cis-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-urea	429.4 (M+H)
112	1-[cis-4-(6-Dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3-(2-ethoxy-phenyl)-urea	413.5 (M+H)
113	1-(4-Benzyloxy-phenyl)-3-[cis-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-urea	475.5 (M+H)
114	3,5-Dibromo-N-[cis-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-benzamide	510.2 (M+H)
115	3-Bromo-4-chloro-N-[cis-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-benzamide	466.2 (M+H)
116	4-Chloro-N-[cis-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3-trifluoromethyl-benzamide	456.2 (M+H)
117	2-(3,5-Bis-trifluoromethyl-phenyl)-N-[cis-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-2-hydroxy-acetamide	520.2 (M+H)
118	N-[cis-4-(2-Dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3-methoxy-benzamide	384.2 (M+H)
119	N-[cis-4-(2-Dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3-trifluoromethyl-benzamide	422.2 (M+H)
120	N-[cis-4-(2-Dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3,5-bis-trifluoromethyl-benzamide	490.4 (M+H)
121	2,2-Difluoro-benzo[1,3]dioxole-5-carboxylic acid [cis-4-(2-dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-amide	434.2 (M+H)
122	4-Cyano-N-[cis-4-(2-dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-benzamide	379.4 (M+H)
123	4-Chloro-N-[cis-4-(2-dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-benzamide	388.2 (M+H)
124	N-[cis-4-(2-Dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3-ethyl-benzamide	382.4 (M+H)
125	N-[cis-4-(2-Dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3,4-difluoro-benzamide	390.4 (M+H)
126	5-Bromo-N-[cis-4-(2-dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-nicotinamide	433.2 (M+H)
127	5-Bromo-furan-2-carboxylic acid [cis-4-(2-dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-amide	422.2 (M+H)
128	3,5-Dibromo-N-[cis-4-(2-dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-benzamide	510.2 (M+H)
129	N-[cis-4-(2-Dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3-ethoxy-benzamide	398.2 (M+H)
130	2-(3,5-Bis-trifluoromethyl-phenyl)-N-[cis-4-(2-dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-2-hydroxy-acetamide	520.4 (M+H)
131	2-(4-Bromo-phenyl)-N-[cis-4-(2-dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-2-hydroxy-acetamide	462.2 (M+H)

Ex. No.	compound name	MS
132	N-[cis-4-(2-Dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3,5-diethoxy-benzamide	442.6 (M+H)
133	3-Bromo-N-[cis-4-(2-dimethylamino-5-methyl-pyrimidin-4-ylamino)-cyclohexyl]-4-fluoro-benzamide	450 (M+H)
134	N-[cis-4-(2-Dimethylamino-6-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3-ethoxy-benzamide	384.2 (M+H)
135	N-[cis-4-(2-Dimethylamino-6-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3-trifluoromethyl-benzamide	422.2 (M+H)
136	N-[cis-4-(2-Dimethylamino-6-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3,5-bis-trifluoromethyl-benzamide	490.4 (M+H)
137	2,2-Difluoro-benzo[1,3]dioxole-5-carboxylic acid [cis-4-(2-dimethylamino-6-methyl-pyrimidin-4-ylamino)-cyclohexyl]-amide	434.4 (M+H)
138	4-Chloro-N-[cis-4-(2-dimethylamino-6-methyl-pyrimidin-4-ylamino)-cyclohexyl]-benzamide	388.2 (M+H)
139	N-[cis-4-(2-Dimethylamino-6-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3-ethyl-benzamide	382.4 (M+H)
140	N-[cis-4-(2-Dimethylamino-6-methyl-pyrimidin-4-ylamino)-cyclohexyl]-4-methyl-benzamide	368.2 (M+H)
141	5-Bromo-N-[cis-4-(2-dimethylamino-6-methyl-pyrimidin-4-ylamino)-cyclohexyl]-nicotinamide	433.2 (M+H)
142	5-Bromo-furan-2-carboxylic acid [cis-4-(2-dimethylamino-6-methyl-pyrimidin-4-ylamino)-cyclohexyl]-amide	422 (M+H)
143	3,5-Dibromo-N-[cis-4-(2-dimethylamino-6-methyl-pyrimidin-4-ylamino)-cyclohexyl]-benzamide	510 (M+H)
144	N-[cis-4-(2-Dimethylamino-6-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3-ethoxy-benzamide	398.2 (M+H)
145	2-(3,5-Bis-trifluoromethyl-phenyl)-N-[cis-4-(2-dimethylamino-6-methyl-pyrimidin-4-ylamino)-cyclohexyl]-2-hydroxy-acetamide	520.4 (M+H)
146	2-(4-Bromo-phenyl)-N-[cis-4-(2-dimethylamino-6-methyl-pyrimidin-4-ylamino)-cyclohexyl]-2-hydroxy-acetamide	462.2 (M+H)
147	N-[cis-4-(2-Dimethylamino-6-methyl-pyrimidin-4-ylamino)-cyclohexyl]-3,5-diethoxy-benzamide	442.4 (M+H)
148	3-Bromo-N-[cis-4-(2-dimethylamino-6-methyl-pyrimidin-4-ylamino)-cyclohexyl]-4-fluoro-benzamide	450 (M+H)
149	N-[cis-4-(6-Dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-3-fluoro-4-trifluoromethyl-benzamide	454.2 (M+H)
150	N-[cis-4-(6-Dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-3-trifluoromethoxy-benzamide	452.2 (M+H)
151	N-[cis-4-(6-Dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-3-methoxy-benzamide	398.2 (M+H)
152	4-Chloro-N-[cis-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-benzamide	402.2 (M+H)

Ex. No.	compound name	MS
153	N-[cis-4-(6-Dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-3-trifluoromethyl-benzamide	436_2 (M+H)
154	N-[cis-4-(6-Dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-4-trifluoromethyl-benzamide	436_2 (M+H)
155	N-[cis-4-(6-Dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-3-methyl-benzamide	382_4 (M+H)
156	N-[cis-4-(6-Dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-3,5-difluoro-benzamide	40◁ (M+H)
157	N-[cis-4-(6-Dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-3-ethyl-benzamide	396_2 (M+H)
158	2,2-Difluoro-benzo[1,3]dioxole-5-carboxylic acid [cis-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-amide	448_2 (M+H)
159	N-[cis-4-(6-Dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-3-fluoro-4-methyl-benzamide	400_2 (M+H)
160	N-[cis-4-(6-Dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-4-fluoro-benzamide	386_2 (M+H)
161	3,4-Dichloro-N-[cis-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-benzamide	436_2 (M+H)
162	4-Bromo-N-[cis-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-benzamide	446_2 (M+H)
163	N-[cis-4-(6-Dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-3,4-difluoro-benzamide	404_2 (M+H)
164	3,5-Dichloro-N-[cis-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-benzamide	436_2 (M+H)
165	3-Chloro-N-[cis-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-4-fluoro-benzamide	420_2 (M+H)
166	N-[cis-4-(6-Dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-4-fluoro-3-methyl-benzamide	400_2 (M+H)
167	3-Chloro-N-[cis-4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexylmethyl]-benzamide	402 (M+H)

Example 168

***N*-{*cis*-4-[(6-Amino-2-methylpyrimidin-4-yl)amino]cyclohexyl}-3,4,5-trifluorobenzamide hydrochloride**

Step A: Synthesis of *N*-(*cis*-4-aminocyclohexyl)-3,4,5-trifluorobenzamide.

To a solution of *tert*-butyl (*cis*-4-aminocyclohexyl)carbamate (44.3 g) in DMF (450 mL) were added 3,4,5-trifluorobenzoic acid (40.1 g), Et_3N (69.2 mL), HOBt-H_2O (47.5 g), and EDC-HCl (43.6 g). The mixture was stirred at ambient temperature for 12 h. To the mixture was added water (1 L) and the suspension was stirred at ambient temperature for 2 h. The precipitate was collected by filtration, washed with water and hexane, and dried at 80 °C under reduced pressure to give a pale brown solid (82.7 g). To a suspension of the above solid in EtOAc (800 mL) was added 4 M hydrogen chloride in EtOAc (600 mL) under 10 °C. The mixture was stirred at ambient temperature for 6 h and concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ (300 mL) and poured into 1 M aqueous NaOH (500 mL). The aqueous layer was extracted with $CHCl_3$ three times. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the title compound (65.3 g).

^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.38-1.91 (m, 8H), 2.97-3.09 (m, 1H), 4.04-4.20 (m, 1H), 6.15-6.27 (m, 1H), 7.35-7.50 (m, 2H); ESI MS *m/z* 273 (M^++1, 100%).

Step B: Synthesis of 6-chloro-2-methylpyrimidin-4-amine.

To a solution of 4,6-dichloro-2-methyl-pyrimidine obtained in step A of example 5 (15.0 g) in 2-propanol (30 mL) was added 28% aqueous NH_3 (30 mL). The mixture was stirred at reflux for 6 hr in a sealed tube and cooled to ambient temperature. The precipitate was collected by filtration, washed with 2-propanol, and dried at 80 °C under reduced pressure to give the title compound (7.58 g).

^{1}H NMR (300 MHz, DMSO-d_6, δ): 2.29 (s, 3H), 6.27 (s, 1H), 7.12 (brs, 2H); ESI MS *m/z* 144 (M^++1, 100%).

Step C: Synthesis of {*cis*-4-[(6-amino-2-methylpyrimidin-4-yl)amino]cyclohexyl}-3,4,5-trifluorobenzamide hydrochloride.

To a suspension of *N*-(*cis*-4-aminocyclohexyl)-3,4,5-trifluorobenzamide (1.20 g) in BuOH (2 mL) was added 6-chloro-2-methylpyrimidin-4-amine (534 mg). The mixture was heated in a microwave synthesizer at 220°C for 30 min. The mixture was diluted with $CHCl_3$ and added to saturated aqueous $NaHCO_3$. The aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtrated, concentrated under reduced pressure, and purified by medium-pressure liquid chromatography (NH-silica gel, 20% to 80% EtOAc in hexane) to give a oil. To a solution of the above oil in EtOAc (10 mL) was added 4 M hydrogen chloride in EtOAc (0.5 mL). The mixture was stirred at ambient temperature for 30 min and concentrated under reduced pressure. A suspension of the residue in Et_2O (10 mL) was stirred at ambient temperature for 2 h. The precipitate was collected by filtration, washed with Et_2O, and dried at 80°C under reduced pressure to give the title compound (627 mg).

^{1}H NMR (300 MHz, DMSO-d_6, δ): 1.60-1.75 (m, 8H), 2.36 (s, 3H), 3.80-4.13 (m, 2H), 5.43-5.78 (m, 1H), 7.16-7.70 (m, 1H), 7.74-7.95 (m, 2H), 8.37-8.48 (m, 1H) ,13.29-13.55 (m, 1H); ESI MS *m/z* 380 [M (free)$^+$+1, 100%].

Example 169

3,4,5-Trifluoro-*N*-(*cis*-4-{[2-methyl-6-(methylamino)pyrimidin-4-yl]amino}cyclohexyl)-benzamide hydrochloride

Step A: Synthesis of 6-chloro-*N*,2-dimethylpyrimidin-4-amine.

To a solution of 4,6-dichloro-2-methyl-pyrimidine obtained in step A of example 5 (15.0 g) in THF (150 mL) was added 40% aqueous $MeNH_2$ (17.9 g) and the mixture was stirred at ambient temperature for 3 h. The mixture was diluted with $CHCl_3$ and added to saturated aqueous $NaHCO_3$. The aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtrated, concentrated under reduced pressure, and dried under reduced pressure to give the title compound (13.6 g).

^{1}H NMR (300 MHz, $CDCl_3$, δ): 2.48 (s, 3H), 2.93 (d, J = 5.1 Hz, 3H), 5.02-5.29 (m, 1H), 6.18 (s, 1H); ESI MS *m/z* 158 (M^++1, 100%).

Step B: Synthesis of 3,4,5-trifluoro-*N*-(*cis*-4-{[2-methyl-6-(methylamino)pyrimidin-4-yl]amino}cyclohexyl)benzamide hydrochloride.

The title compound (312 mg) was prepared from *N*-(*cis*-4-aminocyclohexyl)-3,4,5-trifluorobenzamide obtained in step A of example 168 (952 mg) and 6-chloro-*N*,2-dimethylpyrimidin-4-amine (500 mg) using the procedure for the step C of example 168. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.55-1.91 (m, 8H), 2.22-2.46 (m, 3H), 2.71-2.94 (m, 3H), 3.73-4.11 (m, 2H), 5.36-5.67 (m, 2H), 7.74-7.90 (m, 2H), 8.09-8.52 (m, 2H); ESI MS *m/z* 394 [M (free)$^+$+1, 100%].

Example 170

***N*-(*cis*-4-{[6-(Dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-3,4,5-trifluorobenzamide methanesulfonate**

To a solution of *N*-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-3,4,5-trifluorobenzamide (3.00 g) obtained in example 11 in EtOH (21 mL) was added MsOH (743 mg). The mixture was stirred at ambient temperature for 1 h and 4 °C for 4 h. The precipitate was collected by filtration, washed with cold EtOH, and dried at 80 °C under reduced pressure to give the title compound (3.16 g). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.60-2.08 (m, 8H), 2.48 (s, 3H), 2.92 (s, 3H), 3.07 (brs, 3H), 3.30 (brs, 3H), 3.71-3.80 (m, 1H), 4.07-4.24 (m, 1H), 5.18 (s, 1H), 7.65-7.83 (m, 4H), 12.63 (brs, 1H); ESI MS *m/z* 408 [M (free)$^+$+1, 100%].

Example 171

3-Chloro-*N*-{*cis*-4-[(2,6-dimethylpyrimidin-4-yl)amino]cyclohexyl}-4-fluorobenzamide hydrochloride

Step A: Synthesis of 4-chloro-2,6-dimethylpyrimidine.

A solution of $ZnBr_2$ (4.14 g) in THF (15 mL) was cooled to –60°C and 3 M methylmagnesiumbromide in Et_2O (6.13 mL) was added. The mixture was stirred at –60°C for 1 hr and warmed to ambient temperature. To the mixture were added tetrakis-

(triphenylphosphine)-palladium (1.06 g) and 4,6-dichloro-2-methyl-pyrimidine obtained in step A of example 5 (3.0 g) in THF (15 mL). The mixture was stirred at 60 °C for 8 h. To the mixture was added saturated aqueous NH_4Cl and the aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtered, concentrated under reduced pressure, and purified by medium-pressure liquid chromatography (silica gel, 5% to 16% EtOAc in hexane) to give the title compound (940 mg).

^1H NMR (300 MHz, $CDCl_3$, δ): 2.49 (s, 3H), 2.68 (s, 3H), 7.05 (s, 1H); CI MS *m/z* 143 (M^++1, 100%).

Step B: Synthesis of 3-chloro-*N*-{*cis*-4-[(2,6-dimethylpyrimidin-4-yl)amino]cyclohexyl}-4-fluorobenzamide hydrochloride.

The title compound (454 mg) was prepared from *N*-(*cis*-4-amino-cyclohexyl)-3-chloro-4-fluoro-benzamide obtained in step A of example 31 (520 mg) and 4-chloro-2,6-dimethylpyrimidine (250 mg) using the procedure for the step C of example 168.

^1H NMR (600 MHz, $CDCl_3$, δ): 1.68-2.16 (m, 8H), 2.38 (brs, 3H), 2.62 (s, 3H), 4.10-4.22 (m, 1H), 4.43-4.53 (m, 1H), 6.80-6.91 (m, 1H), 7.08-7.18 (m, 2H), 7.75-7.86 (m, 1H), 7.92-8.12 (m, 1H), 8.90-9.06 (m, 1H); ESI MS *m/z* 377 [M (free)$^+$+1, 100%].

Example 172

***N*-{*cis*-4-[(6-Chloro-2-methylpyrimidin-4-yl)amino]cyclohexyl}-3,4,5-trifluorobenzamide**

To a suspension of *N*-(*cis*-4-aminocyclohexyl)-3,4,5-trifluorobenzamide obtained in step A of example 168 (16.7 g) in BuOH (9.1 mL) were added 4,6-dichloro-2-methyl-pyrimidine obtained in step A of example 5 (9.10 g) and $iPrNEt_2$ (10.7 mL). The mixture was stirred at reflux for 1.5 h. The mixture was diluted with $CHCl_3$ and added to saturated aqueous $NaHCO_3$. The aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtrated, concentrated under reduced pressure, and purified by medium-pressure liquid chromatography (NH-silica gel, 33% to

66% EtOAc in hexane) to give the title compound (21.0 g).

^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.56-2.03 (m, 8H), 2.47 (s, 3H), 3.74-3.92 (m, 1H), 4.03-4.18 (m, 1H), 5.08-5.24 (m, 1H), 6.08 (d, J = 7.3 Hz, 1H), 6.18 (s, 1H), 7.33-7.50 (m, 2H); ESI MS *m/z* 399 (M^++1, 100%).

Example 173

***N*-(*cis*-4-{[6-(Cyclopropylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-3,4,5-trifluorobenzamide hydrochloride**

To a suspension of *N*-{*cis*-4-[(6-chloro-2-methylpyrimidin-4-yl)amino]cyclohexyl}-3,4,5-trifluorobenzamide obtained in example 172 (250 mg) in 3-methyl-butan-1-ol (0.5 mL) was added cyclopropylamine (43 mg). The mixture was stirred at 190 °C for 1.5 h in a sealed tube. The mixture was diluted with $CHCl_3$ and added to saturated aqueous $NaHCO_3$. The aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtrated, concentrated under reduced pressure, and purified by medium-pressure liquid chromatography (NH-silica gel, 20% to 50% EtOAc in hexane and silica gel, 2% to 9% MeOH in $CHCl_3$) to give a colorless oil. To a solution of the above oil in EtOAc (10 mL) was added 4 M hydrogen chloride in EtOAc (0.5 mL). The mixture was stirred at ambient temperature for 30 min and concentrated under reduced pressure. A suspension of the residue in Et_2O (10 mL) was stirred at ambient temperature for 2 hr. The precipitate was collected by filtration, washed with Et_2O, and dried at 80°C under reduced pressure to give the title compound (90 mg).

^{1}H NMR (300 MHz, $CDCl_3$, δ): 0.62-0.74 (m, 2H), 0.88-1.00 (m, 2H), 1.72-2.02 (m, 8H), 2.45 (s, 3H), 2.50-2.64 (m, 1H), 3.71-3.87 (m, 1H), 4.03-4.19 (m, 1H), 5.52 (s, 1H), 6.80-6.96 (m, 1H), 7.48-7.62 (m, 2H); ESI MS *m/z* 420 [M (free)$^+$+1, 100%].

Example 174

3,4,5-Trifluoro-*N*-[*cis*-4-({2-methyl-6-[methyl(phenyl)amino]pyrimidin-4-yl}amino)-cyclohexyl]benzamide hydrochloride

The title compound (210 mg) was prepared from *N*-{*cis*-4-[(6-chloro-2-methylpyrimidin-4-yl)amino]cyclohexyl}-3,4,5-trifluorobenzamide obtained in example 172 (250 mg) and *N*-methylaniline (81 mg) using the procedure for the example 173. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.50-1.91 (m, 8H), 2.55 (s, 3H), 3.31-3.40 (m, 1H), 3.54 (s, 3H), 3.95-4.09 (m, 1H), 4.96 (s, 1H), 6.81 (d, J = 8.4 Hz, 1H), 7.21-7.27 (m, 2H), 7.40-7.58 (m, 4H), 8.43 (d, J = 8.4 Hz, 1H); ESI MS *m/z* 470 [M (free)$^+$+1, 100%].

Example 175

***N*-[*cis*-4-({6-[Benzyl(methyl)amino]-2-methylpyrimidin-4-yl}amino)cyclohexyl]-3,4,5-trifluorobenzamide hydrochloride**

The title compound (121 mg) was prepared from *N*-{*cis*-4-[(6-chloro-2-methylpyrimidin-4-yl)amino]cyclohexyl}-3,4,5-trifluorobenzamide obtained in example 172 (250 mg) and *N*-methylbenzylamine (91 mg) using the procedure for the example 173. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.57-2.07 (m, 8H), 2.51 (s, 3H), 2.98 (s, 3H), 3.28-3.45 (m, 1H), 3.68-3.81 (m, 1H), 3.98-4.20 (m, 1H), 4.94-5.23 (m, 2H), 6.93-7.04 (m, 1H), 7.12-7.24 (m, 2H), 7.30-7.42 (m, 3H), 7.48-7.61 (m, 2H), 8.54-8.67 (m, 1H), 13.78-13.89 (m, 1H); ESI MS *m/z* 484 [M (free)$^+$+1, 100%].

Example 176

***N*-[*cis*-4-({6-[Ethyl(methyl)amino]-2-methylpyrimidin-4-yl}amino)cyclohexyl]-3,4,5-trifluorobenzamide hydrochloride**

The title compound (71 mg) was prepared from *N*-{*cis*-4-[(6-chloro-2-methylpyrimidin-4-yl)amino]cyclohexyl}-3,4,5-trifluorobenzamide obtained in example 172 (250 mg) and *N*-ethylmethylamine (44 mg) using the procedure for the example 173. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.06-1.35 (m, 3H), 1.62-2.11 (m, 8H), 2.48 (s, 3H), 2.96-3.49 (m, 4H), 3.67-3.85 (m, 2H), 4.01-4.20 (m, 1H), 5.04-5.20 (m, 1H), 6.98 (d, J = 8.5 Hz, 1H), 7.47-7.63 (m, 2H), 8.36-8.55 (m, 1H), 13.57-13.77 (m, 1H); ESI MS *m/z* 422 [M (free)$^+$+1, 100%].

Example 177

***N*-(*cis*-4-{[6-(Dimethylamino)-2-ethylpyrimidin-4-yl]amino}cyclohexyl)-3,4,5-trifluorobenzamide hydrochloride**

The title compound (126 mg) was prepared from *N*-{*cis*-4-[(6-chloro-2-methylpyrimidin-4-yl)amino]cyclohexyl}-3,4,5-trifluorobenzamide obtained in step A of example 168 (403 mg) and (6-chloro-2-ethyl-pyrimidin-4-yl)-dimethyl-amine in step B of example 32 (250 mg) using the procedure for the step C of example 168.

^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.36 (t, J = 7.5 Hz, 3H), 1.65-2.02 (m, 8H), 2.75 (q, J = 7.5 Hz, 2H), 2.97-3.41 (m, 6H), 3.68-3.77 (m, 1H), 4.02-4.17 (m, 1H), 5.15 (s, 1H), 6.89 (d, J = 8.7 Hz, 1H), 7.48-7.60 (m, 2H), 8.58 (d, J = 8.5 Hz, 1H), 13.48-13.72 (m, 1H); ESI MS *m/z* 422 [M (free)$^+$+1, 100%].

Example 178

3-Chloro-*N*-(*cis*-4-{[6-(dimethylamino)-2-phenylpyrimidin-4-yl]amino}cyclohexyl)-4-fluorobenzamide hydrochloride

Step A: Synthesis of 6-chloro-*N*,*N*-dimethyl-2-phenylpyrimidin-4-amine.

To a solution of 4,6-dichloro-2-phenylpyrimidine (2.00 g) in THF (10 mL) was added 50% aqueous Me_2NH (2.30 mL) and the mixture was stirred at ambient temperature for 3 h. The mixture was diluted with $CHCl_3$ and added to saturated aqueous $NaHCO_3$. The aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtrated, concentrated under reduced pressure, and dried under reduced pressure to give the title compound (2.05 g).

^{1}H NMR (300 MHz, $CDCl_3$, δ): 3.19 (brs, 6H), 6.34 (s, 1H), 7.39-7.49 (m, 3H), 8.35-8.45 (m, 2H); ESI MS *m/z* 234 (M^++1, 100%).

Step B: Synthesis of 3-chloro-*N*-(*cis*-4-{[6-(dimethylamino)-2-phenylpyrimidin-4-yl]amino}cyclohexyl)-4-fluorobenzamide hydrochloride.

The title compound (85 mg) was prepared from 6-chloro-*N*,*N*-dimethyl-2-phenylpyrimidin-4-amine (250 mg) and *N*-(*cis*-4-amino-cyclohexyl)-3-chloro-4-fluoro-

benzamide obtained in step A of example 31 (319 mg) using the procedure for the step C of example 168.

^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.69-2.13 (m, 8H), 3.05-3.53 (m, 6H), 3.75-3.84 (m, 1H), 4.07-4.23 (m, 1H), 5.26 (s, 1H), 6.56-6.67 (m, 1H), 7.18 (t, J = 8.6 Hz, 1H), 7.51-7.75 (m, 4H), 7.95 (d, J = 8.5 Hz, 1H), 8.48 (d, J = 6.5 Hz, 2H), 9.25-9.37 (m, 1H), 13.71-13.88 (m, 1H); ESI MS *m/z* 468 [M (free)$^+$+1, 100%].

Example 179

***N*-(*cis*-4-{[2-Benzyl-6-(dimethylamino)pyrimidin-4-yl]amino}cyclohexyl)-3-chloro-4-fluorobenzamide hydrochloride**

Step A: Synthesis of 2-benzyl-6-chloro-*N*,*N*-dimethylpyrimidin-4-amine.

The title compound (2.02 g) was prepared from 2-benzyl-4,6-dichloropyrimidine (2.00 g) and 50% aqueous Me_2NH (2.20 mL) using the procedure for the step A of example 178.

^{1}H NMR (300 MHz, $CDCl_3$, δ): 3.06 (s, 6H), 4.02 (s, 2H), 6.23 (s, 1H), 7.16-7.43 (m, 5H); ESI MS *m/z* 248 (M^++1, 100%).

Step B: Synthesis of *N*-(*cis*-4-{[2-benzyl-6-(dimethylamino)pyrimidin-4-yl]amino}cyclohexyl)-3-chloro-4-fluorobenzamide hydrochloride.

The title compound (132 mg) was prepared from 2-benzyl-6-chloro-*N*,*N*-dimethylpyrimidin-4-amine (250 mg) and *N*-(*cis*-4-amino-cyclohexyl)-3-chloro-4-fluoro-benzamide obtained in step A of example 31 (301 mg) using the procedure for the step C of example 168.

^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.65-2.04 (m, 8H), 2.94-3.38 (m, 6H), 3.63-3.75 (m, 1H), 3.98 (s, 2H), 4.02-4.21 (m, 1H), 5.11 (s, 1H), 6.63 (d, J = 8.1 Hz, 1H), 7.14-7.38 (m, 4H), 7.46-7.54 (m, 2H), 7.67-7.75 (m, 1H), 7.91-7.97 (m, 1H), 8.57 (d, J = 7.9 Hz, 1H); ESI MS *m/z* 482 [M (free)$^+$+1, 100%].

Example 180

3-Chloro-*N*-(*cis*-4-{[6-(dimethylamino)-2,5-dimethylpyrimidin-4-yl]amino}cyclohexyl)-4-fluorobenzamide hydrochloride

Step A: Synthesis of 2,5-dimethylpyrimidine-4,6-diol.

To a solution of Na (1.39 g) in EtOH (42 mL) were added diethyl methylmalonate (5.00 g) and acetamidine hydrochloride (2.71 g). The mixture was stirred at reflux for 2.5 h and cooled to ambient temperature. The precipitate was collected by filtration, washed with EtOH, and dried at 80°C under reduced pressure to give a white solid. To a solution of the above solid in H_2O (30 mL) was added conc. HCl (2.5 mL) and the mixture was stirred at 4 °C for 1 h. The precipitate was collected by filtration, washed with H_2O (twice), EtOH (twice), and Et_2O (twice), and dried at 80°C under reduced pressure to give the title compound (3.02 g).

^{1}H NMR (300 MHz, DMSO-d_6, δ): 1.69 (s, 3H), 2.19 (s, 3H), 11.42-11.66 (m, 2H); ESI MS *m/z* 139 (M^--1, 100%).

Step B: Synthesis of 4,6-dichloro-2,5-dimethylpyrimidine.

A mixture of 2,5-dimethylpyrimidine-4,6-diol (3.02 g), $POCl_3$ (4.2 mL), and *N*,*N*-dimethylaniline (3.0 mL) was stirred at reflux for 1.5 hr and cooled to ambient temperature. The mixture was poured into ice water (20 mL) and stirred for 2 h. The precipitate was collected by filtration, washed with H_2O and hexane, and dried at 60°C to give the title compound (1.66 g).

^{1}H NMR (300 MHz, $CDCl_3$, δ): 2.45 (s, 3H), 2.66 (s, 3H); CI MS *m/z* 177 (M^+, 100%).

Step C: Synthesis of 6-chloro-*N*,*N*,2,5-tetramethylpyrimidin-4-amine.

The title compound (1.65 g) was prepared from 4,6-dichloro-2,5-dimethylpyrimidine (1.66 g) and 50% aqueous Me_2NH (2.40 mL) using the procedure for the step A of example 178.

^{1}H NMR (300 MHz, $CDCl_3$, δ): 2.25 (s, 3H), 2.48 (s, 3H), 3.02 (s, 6H); ESI MS *m/z* 186 (M^++1, 100%).

Step D: Synthesis of 3-chloro-*N*-(*cis*-4-{[6-(dimethylamino)-2,5-dimethylpyrimidin-4-

yl]amino}cyclohexyl)-4-fluorobenzamide hydrochloride.

The title compound (231 mg) was prepared from 6-chloro-*N*,*N*,2,5-tetramethylpyrimidin-4-amine (300 mg) and *N*-(*cis*-4-amino-cyclohexyl)-3-chloro-4-fluoro-benzamide obtained in step A of example 31 (481 mg) using the procedure for the step C of example 168.

^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.63-2.19 (m, 11H), 2.56 (brs, 3H), 3.18 (s, 6H), 3.92-4.27 (m, 2H), 6.82-6.94 (m, 1H), 7.10-7.25 (m, 2H), 7.80-7.88 (m, 1H), 8.03 (d, J = 6.2 Hz, 1H); ESI MS *m/z* 420 [M (free)$^+$+1, 100%].

Example 181

3-Chloro-*N*-(*cis*-4-{[6-(dimethylamino)-5-fluoro-2-methylpyrimidin-4-yl]amino}cyclohexyl)-4-fluorobenzamide hydrochloride

Step A: Synthesis of 5-fluoro-2-methylpyrimidine-4,6-diol.

The title compound (3.21 g) was prepared from diethyl fluoromalonate (5.27 g) and acetamidine hydrochloride (2.80 g) using the procedure for the step A of example 180.

^{1}H NMR (300 MHz, DMSO-d_6, δ): 2.22 (d, J = 0.9 Hz, 3H); ESI MS *m/z* 143 (M^--1, 100%).

Step B: Synthesis of 4,6-dichloro-5-fluoro-2-methylpyrimidine.

The title compound (3.13 g) was prepared from 5-fluoro-2-methylpyrimidine-4,6-diol (3.20 g) using the procedure for the step B of example 180.

^{1}H NMR (200 MHz, $CDCl_3$, δ): 2.69 (d, J = 1.3 Hz, 3H); CI MS *m/z* 181 (M^++1, 100%).

Step C: Synthesis of 6-chloro-5-fluoro-*N*,*N*,2-trimethylpyrimidin-4-amine.

The title compound (2.02 g) was prepared from 4,6-dichloro-5-fluoro-2-methylpyrimidine (3.10 g) using the procedure for the step C of example 180.

^{1}H NMR (300 MHz, $CDCl_3$, δ): 2.44 (d, J = 0.9 Hz, 3H), 3.22 (d, J = 2.5 Hz, 6H); ESI MS *m/z* 190 (M^++1, 100%).

Step D: Synthesis of 3-chloro-*N*-(cis-4-{[6-(dimethylamino)-5-fluoro-2-methylpyrimidin-4-yl]amino}cyclohexyl)-4-fluorobenzamide hydrochloride.

The title compound (135 mg) was prepared from 6-chloro-5-fluoro-*N*,*N*,2-trimethylpyrimidin-4-amine (300 mg) and *N*-(*cis*-4-amino-cyclohexyl)-3-chloro-4-fluoro-benzamide obtained in step A of example 31 (471 mg) using the procedure for the step C of example 168.

^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.70-2.13 (m, 8H), 2.48 (s, 3H), 3.29 (d, J = 3.1 Hz, 6H), 4.06-4.21 (m, 2H), 6.52-6.70 (m, 1H), 7.12-7.25 (m, 1H), 7.66-8.02 (m, 3H); ESI MS *m/z* 424 [M (free)$^+$+1, 100%].

Example 182

3-Chloro-*N*-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-4-fluorobenzenesulfonamide hydrochloride

The title compound (271 mg) was prepared from *N*-(*cis*-4-amino-cyclohexyl)-2,*N'*,*N'*-trimethyl-pyrimidine-4,6-diamine obtained in step C of example 6 (250 mg) and 3-chloro-4-fluorobenzenesulfonyl chloride (275 mg) using the procedure for the example 7.

^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.57-1.96 (m, 8H), 2.47 (s, 3H), 2.94-3.39 (m, 7H), 3.50-3.61 (m, 1H), 5.08 (s, 1H), 5.83 (d, J = 6.7 Hz, 1H), 7.21-7.31 (m, 1H), 7.85-7.93 (m, 1H), 8.00-8.06 (m, 1H), 8.38 (d, J = 8.2 Hz, 1 H); ESI MS *m/z* 442 [M (free)$^+$+1, 100%].

Example 183

***N*-(3-Chloro-4-fluorophenyl)-*N'*-(*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)thiourea hydrochloride**

To a solution of *N*-(*cis*-4-amino-cyclohexyl)-2,*N'*,*N'*-trimethyl-pyrimidine-4,6-diamine obtained in step C of example 6 (250 mg) in DMSO (2 mL) was added 3-chloro-4-fluorophenyl isothiocyanate (206 mg) in DMSO (1 mL). The mixture was stirred at ambient temperature for 14 h and poured into water. The precipitate was collected by filtration, washed with water, and purified by medium-pressure liquid chromatography (NH-silica gel, 20% to 50% EtOAc in hexane). To a solution of the above material in EtOAc (10 mL) was added 4 M hydrogen chloride in EtOAc (0.5 mL). The mixture was

stirred at ambient temperature for 1 h and concentrated under reduced pressure. A suspension of the residue in Et_2O (10 mL) was stirred at ambient temperature for 3 h. The precipitate was collected by filtration, washed with Et_2O, and dried at 80 °C under reduced pressure to give the title compound (186 mg).

^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.70-2.12 (m, 8H), 2.40 (s, 3H), 2.95-3.40 (m, 6H), 3.46-3.61 (m, 1H), 4.38-4.54 (m, 1H), 5.09 (brs, 1H), 6.99-7.13 (m, 1H), 7.37-7.57 (m, 2H), 7.65-7.77 (m, 1H), 7.88-8.01 (m, 1H), 9.16-9.29 (m, 1H), 13.26-13.42 (m, 1H); ESI MS *m/z* 437 [M (free)$^+$+1, 100%].

Example 184

4-Bromophenyl (*cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)carbamate

To a solution of *N*-(*cis*-4-amino-cyclohexyl)-2,*N'*,*N'*-trimethyl-pyrimidine-4,6-diamine obtained in step C of example 6 (250 mg) in $CHCl_3$ (3 mL) were added Et_3N (0.21 mL) and 4-bromophenyl chloroformate (283 mg). The mixture was stirred at ambient temperature for 14 hr. The reaction was quenched with saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtered, concentrated under reduced pressure, and purified by medium-pressure liquid chromatography (silica gel, 2% to 9% MeOH in $CHCl_3$) to give the title compound (100 mg).

^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.54-1.95 (m, 8H), 2.36 (s, 3H), 3.06 (s, 6H), 3.58-3.81 (m, 2H), 4.66-4.77 (m, 1H), 4.96-5.04 (m, 1H), 5.15 (s, 1H), 7.03 (d, J = 9.0 Hz, 2H), 7.46 (d, J = 8.9 Hz, 2H); ESI MS *m/z* 448 (M^++1, 100%).

Example 185

3-Chloro-*N*-{*cis*-4-[(2,6-dimethoxypyrimidin-4-yl)amino]cyclohexyl}-4-fluorobenzamide hydrochloride

The title compound (16 mg) was prepared from 6-chloro-2,4-dimethoxypyrimidine (250 mg) and *N*-(*cis*-4-amino-cyclohexyl)-3-chloro-4-fluoro-benzamide obtained in step A of example 31 (426 mg) using the procedure for the step C of example 168.

^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.66-2.04 (m, 8H), 3.64-3.78 (m, 1H), 4.03 (s, 3H), 4.06-4.22 (m, 4H), 5.52 (s, 1H), 6.71-6.86 (m, 1H), 7.12-7.24 (m, 1H), 7.68-7.79 (m, 1H), 7.95 (d, J = 8.2 Hz, 1H), 9.14-9.28 (m, 1H); ESI MS *m/z* 409 [M (free)$^+$+1, 40%], 423 [M (free)$^+$+15, 100%].

Example 186

3-Chloro-4-fluoro-*N*-[*cis*-4-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)cyclohexyl]benzamide hydrochloride

The title compound (113 mg) was prepared from 4-chloro-7*H*-pyrrolo[2,3-d]pyrimidine (300 mg) and *N*-(*cis*-4-amino-cyclohexyl)-3-chloro-4-fluoro-benzamide obtained in step A of example 31 (582 mg) using the procedure for the step C of example 168.

^{1}H NMR (300 MHz, DMSO-d_6, δ): 1.61-2.09 (m, 8H), 3.91-4.17 (m, 2H), 7.01-7.12 (m, 1H), 7.35-7.47 (m, 1H), 7.49-7.59 (m, 1H), 7.88-7.98 (m, 1H), 8.11-8.18 (m, 1H), 8.25-8.41 (m, 2H), 9.10-9.33 (m, 1H), 12.58-12.78 (m, 1H); ESI MS *m/z* 388 [M (free)$^+$+1, 100%].

Example 187

3-Chloro-4-fluoro-*N*-{*cis*-4-[(7-methyl-7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)amino]cyclohexyl}-benzamide hydrochloride

Step A: Synthesis of 4-chloro-7-methyl-7H-pyrrolo[2,3-d]pyrimidine.

To a solution of 4-chloro-7*H*-pyrrolo[2,3-d]pyrimidine (1.00 g) in DMF (10 mL) under N_2 was added 60% NaH in oil (287 mg) and the mixture was stirred at ambient temperature for 10 min. Iodomethane (0.45 mL) was added to the mixture and the mixture was stirred at ambient temperature for 3 h. The reaction was quenched with saturated

aqueous NH_4Cl and the aqueous layer was extracted with EtOAc (three times). The combined organic layer was dried over $MgSO_4$, filtered, concentrated under reduced pressure, and purified by medium-pressure liquid chromatography (silica gel, 50% EtOAc in hexane) to give the title compound (999 mg).

^1H NMR (300 MHz, $CDCl_3$, δ): 3.90 (s, 3H), 6.61 (d, J = 3.6 Hz, 1H), 7.22 (d, J = 3.6 Hz, 1H), 8.65 (s, 1 H); ESI MS *m/z* 168 [M (free)$^+$+1, 100%].

Step B: Synthesis of 3-chloro-4-fluoro-*N*-{*cis*-4-[(7-methyl-7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)amino]cyclohexyl}benzamide hydrochloride.

The title compound (765 mg) was prepared from 4-chloro-7-methyl-7H-pyrrolo[2,3-d]pyrimidine (400 mg) and *N*-(*cis*-4-amino-cyclohexyl)-3-chloro-4-fluoro-benzamide obtained in step A of example 31 (711 mg) using the procedure for the step C of example 168.

^1H NMR (300 MHz, DMSO-d_6, δ): 1.64-2.11 (m, 8H), 3.81 (s, 3H), 3.91-4.23 (m, 2H), 7.00-7.17 (m, 1H), 7.40-7.59 (m, 2H), 7.87-7.98 (m, 1H), 8.14 (dd, J = 7.1, 2.2 Hz, 1H), 8.29-8.41 (m, 2H), 9.17-9.37 (m, 1H); ESI MS *m/z* 402 [M (free)$^+$+1, 100%].

Example 188

3,4,5-Trifluoro-*N*-{*cis*-4-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]cyclohexyl}benzamide hydrochloride

The title compound (168 mg) was prepared from *N*-(*cis*-4-aminocyclohexyl)-3,4,5-trifluorobenzamide obtained in step A of example 168 (487 mg) and 4-chloro-7-methyl-7H-pyrrolo[2,3-d]pyrimidine (250 mg) using the procedure for the step C of example 168.

^1H NMR (300 MHz, DMSO-d_6, δ): 1.60-2.15 (m, 8H), 3.81 (s, 3H), 3.90-4.26 (m, 2H), 6.94-7.17 (m, 1H), 7.35-7.53 (m, 1H), 7.73-7.98 (m, 2H), 8.22-8.47 (m, 2H), 9.14-9.42 (m, 1H); ESI MS *m/z* 404 [M (free)$^+$+1, 100%].

Example 189

3-Chloro-*N*-{*cis*-4-[(7-ethyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]cyclohexyl}-4-

fluorobenzamide hydrochloride

Step A: Synthesis of 4-chloro-7-ethyl-7H-pyrrolo[2,3-d]pyrimidine.

The title compound (577 mg) was prepared from 4-chloro-7*H*-pyrrolo[2,3-d]pyrimidine (500 mg) and iodoethane (0.31 mL) using the procedure for the step A of example 187.

^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.50 (t, J = 7.3 Hz, 3H), 4.34 (q, J = 7.3 Hz, 2H), 6.61 (d, J = 3.6 Hz, 1H), 7.27 (d, J = 3.6 Hz, 1H), 8.64 (s, 1H); ESI MS *m/z* 182 (M^++1, 100%).

Step B: Synthesis of 3-chloro-*N*-{*cis*-4-[(7-ethyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]cyclohexyl}-4-fluorobenzamide hydrochloride.

The title compound (299 mg) was prepared from 4-chloro-7-ethyl-7H-pyrrolo[2,3-d]-pyrimidine (250 mg) and *N*-(*cis*-4-amino-cyclohexyl)-3-chloro-4-fluoro-benzamide obtained in step A of example 31 (410 mg) using the procedure for the step C of example 168.

^{1}H NMR (300 MHz, DMSO-d_6, δ): 1.37 (t, J = 7.2 Hz, 3H), 1.63-2.08 (m, 8H), 3.92-4.20 (m, 2H), 4.26 (q, J = 7.3 Hz, 2H), 7.03-7.13 (m, 1H), 7.47-7.59 (m, 2H), 7.88-7.97 (m, 1H), 8.14 (dd, J = 7.2, 2.1 Hz, 1H), 8.27-8.39 (m, 2H), 9.18-9.35 (m, 1H); ESI MS *m/z* 416 [M (free)$^+$+1, 100%].

Example 190

3-Chloro-4-fluoro-*N*-{*cis*-4-[(9-methyl-9H-purin-6-yl)amino]cyclohexyl}benzamide hydrochloride

Step A: Synthesis of 6-chloro-9-methyl-9*H*-purine.

The title compound (1.08 g) was prepared from 6-chloro-9*H*-purine (2.00 g) and iodomethane (0.96 mL) using the procedure for the step A of example 187.

^{1}H NMR (300 MHz, $CDCl_3$, δ): 3.95 (s, 3H), 8.12 (s, 1H), 8,78 (s, 1H); ESI MS *m/z* 182 (M^++1, 100%).

Step B: Synthesis of 3-chloro-4-fluoro-*N*-{*cis*-4-[(9-methyl-9H-purin-6-yl)amino]-cyclohexyl}benzamide hydrochloride.

The title compound (170 mg) was prepared from 6-chloro-9-methyl-9*H*-purine (250 mg) and *N*-(*cis*-4-amino-cyclohexyl)-3-chloro-4-fluoro-benzamide obtained in step A of example 31 (410 mg) using the procedure for the step C of example 168.

^{1}H NMR (300 MHz, DMSO-d_6, δ): 1.61-2.06 (m, 8H), 3.83 (s, 3H), 3.86-4.31 (m, 2H), 4.72-4.98 (m, 1H), 7.48-7.59 (m, 1H), 7.86-7.95 (m, 1H), 8.11 (dd, J = 7.3, 2.2 Hz, 1H), 8.20-8.61 (m, 3H); ESI MS *m/z* 403 [M (free)$^+$+1, 90%], 425 [M (free)$^+$+23, 100%].

Example 191

***cis*-*N*-(3-Chloro-4-fluorophenyl)-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexanecarboxamide hydrochloride**

Step A: Synthesis of *cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}-cyclohexanecarboxylic acid.

To a suspension of (6-chloro-2-methyl-pyrimidin-4-yl)-dimethyl-amine obtained in step B of example 5 (20.0 g) in toluene (300 mL) under N_2 were added *cis*-4-amino-cyclohexanecarboxylic acid (16.7 g), biphenyl-2-yl(di-tert-butyl)phosphine (346 mg), palladium(II)acetate (260 mg), and sodium tert-butoxide (21.6 g). The mixture was stirred at reflux for 6 h and cooled to ambient temperature. To the mixture was added 1 M aqueous NaOH (300 mL) and the two layers were separated. The aqueous layer was washed with EtOAc. The aqueous layer was cooled on an ice-bath and c.HCl (15 mL) was added (pH = 6). The precipitate was collected by filtration, washed with H_2O and EtOAc, and dried at 80°C under reduced pressure to give the title compound (22.1 g).

^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.64-2.16 (m, 8H), 2.35-2.48 (m, 4H), 3.10 (s, 6H), 3.46-3.59 (m, 1H), 5.11 (s, 1H), 8.74-8.84 (m, 1H); ESI MS *m/z* 279 (M^++1, 100%).

Step B: Synthesis of *cis*-*N*-(3-chloro-4-fluorophenyl)-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexanecarboxamide hydrochloride.

To a suspension of *cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexanecarboxylic acid (180 mg) and 3-chloro-4-fluoroaniline (114 mg) in DMF (2 mL) were added Et_3N (0.22 mL), HOBt-H_2O (150 mg), and EDC-HCl (150 mg).

The mixture was stirred at ambient temperature for 14 h. To the mixture was added water (20 mL) and the aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtrated, concentrated under reduced pressure, and purified by medium-pressure liquid chromatography (NH-silica gel, 20% to 50% EtOAc in hexane) to give a colorless oil. To a solution of the above oil in EtOAc (10 mL) was added 4 M hydrogen chloride in EtOAc (0.5 mL). The mixture was stirred at ambient temperature for 1 h and concentrated. The residue was suspended in Et_2O (10 mL) and the suspension was stirred at ambient temperature for 4 h. The precipitate was collected by filtration, washed with Et_2O, and dried at 80°C under reduced pressure to give the title compound (27 mg).

^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.53-1.73 (m, 2H), 1.81-2.02 (m, 4H), 2.13-2.34 (m, 2H), 2.37-2.58 (m, 4H), 3.03-3.36 (m, 6H), 3.76-3.89 (m, 1H), 5.17 (s, 1H), 6.96-7.12 (m, 1H), 7.64-7.77 (m, 1H), 8.02-8.22 (m, 1H), 8.80-8.93 (m, 1H), 9.30-9.46 (m, 1H); ESI MS *m/z* 406 [M (free)$^+$+1, 100%].

Example 192

***cis*-*N*-(3,4-Difluorophenyl)-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexanecarboxamide hydrochloride**

To a suspension of *cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}-cyclohexanecarboxylic acid obtained in step A of example 191 (2.1 g) in $CHCl_3$ (2 1 mL) were added thionyl chloride (1.21 mL) and DMF (6 mg). The mixture was stirred at reflux for 1.5 h, concentrated under reduced pressure, and the residue was dissolved in $CHCl_3$ (4.9 mL). To a solution of 3,4-difluoroaniline (223 mg) in $CHCl_3$ (3 mL) were added Et_3N (0.42 mL) and above acid chloride in $CHCl_3$ (1 mL). The mixture was stirred at ambient temperature for 14 h and added to saturated aqueous $NaHCO_3$. The aqueous layer was extracted with $CHCl_3$ (three times). The combined organic layer was dried over $MgSO_4$, filtrated, concentrated under reduced pressure, and purified by medium-pressure liquid chromatography (NH-silica gel, 11% to 50% EtOAc in hexane) to give a colorless oil. To

a solution of the above oil in EtOAc (10 mL) was added 4 M hydrogen chloride in EtOAc (0.5 mL). The mixture was stirred at ambient temperature for 1 h and concentrated under reduced pressure. A suspension of the residue in Et_2O (10 mL) was stirred at ambient temperature for 4 hr. The precipitate was collected by filtration, washed with Et_2O, and dried at 80°C under reduced pressure to give the title compound (102 mg).

^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.51-2.37 (m, 8H), 2.40-2.55 (s, 4H), 3.07 (brs, 3H), 3.31 (brs, 3H), 3.77-3.91 (m, 1H), 5.18 (s, 1H), 6.98-7.12 (m, 1H), 7.56-7.66 (m, 1H), 7.96-8.07 (m, 1H), 8.82 (d, J = 9.8 Hz, 1H), 9.21-9.28 (m, 1H), 13.10-13.26 (m, 1H); ESI MS *m/z* 390 [M (free)$^+$+1, 100%].

Example 193

***cis*-4-{[6-(Dimethylamino)-2-methylpyrimidin-4-yl]amino}-*N*-(3,4,5-trifluorophenyl)-cyclohexanecarboxamide hydrochloride**

The title compound (173 mg) was prepared from 3,4,5-trifluoroaniline (254 mg) using the procedure for the example 192.

^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.54-1.72 (m, 2H), 1.81-2.01 (m, 4H), 2.15-2.36 (m, 2H), 2.40-2.55 (m, 4H), 3.07 (brs, 3H), 3.31 (brs, 3H), 3.80-3.90 (m, 1H), 5.18 (s, 1H), 7.69-7.81 (m, 2H), 8.79 (d, J = 9.6 Hz, 1H), 9.37 (brs, 1H), 13.05 (brs, 1H); ESI MS *m/z* 408 [M (free)$^+$+1, 100%].

Example 194

3-Chloro-4-fluorophenyl *cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}-cyclohexanecarboxylate hydrochloride

The title compound (4 mg) was prepared from 3-chloro-4-fluorophenol (254 mg) using the procedure for the example 192.

^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.61-2.33 (m, 8H), 2.38-2.56 (m, 3H), 2.60-2.77 (m, 1H), 2.91-3.44 (m, 6H), 3.48-3.71 (m, 1H), 5.10 (s, 1H), 6.91-7.34 (m, 3H), 8.38-8.55 (m, 1H); ESI MS *m/z* 407 [M (free)$^+$+1, 100%].

Example 195

***cis*-*N*-(3,5-Dichlorophenyl)-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}-cyclohexanecarboxamide hydrochloride**

The title compound (35 mg) was prepared from 3,5-dichlorophenol (282 mg) using the procedure for the example 192.

^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.72-2.31 (m, 8H), 2.49 (s, 3H), 2.60-2.73 (m, 1H), 2.97-3.41 (m, 6H), 3.52-3.68 (m, 1H), 5.11 (s, 1H), 7.08 (d, J = 1.9 Hz, 2H), 7.21-7.24 (m, 1H), 8.49 (d, J = 7.1 Hz, 1H); ESI MS *m/z* 423 [M (free)$^+$+1, 100%].

Example 196

3,4-Difluorophenyl *cis*-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}-cyclohexanecarboxylate hydrochloride

The title compound (3 mg) was prepared from 3,4-difluorophenol (225 mg) using the procedure for the example 192.

^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.69-2.32 (m, 8H), 2.49 (s, 3H), 2.58-2.77 (m, 1H), 2.93-3.41 (m, 6H), 3.51-3.67 (m, 1H), 5.11 (s, 1H), 6.82-7.24 (m, 3H), 8.32-8.58 (m, 1H); ESI MS *m/z* 391 [M (free)$^+$+1, 100%].

Example 197-274

To a suspension of poly(4-vinylpyridine) (150 μL) in $CHCl_3$ (200 μL) were added *N*-(*cis*-4-amino-cyclohexyl)-2,*N'*,*N'*-trimethyl-pyrimidine-4,6-diamine obtained in step C of example 6 (60 μmol) in $CHCl_3$ (200 μL) and acid chloride (120 μmol) in $CHCl_3$ (200 μL) at ambient temperature. After stirring at the same temperature for 14 h, the mixture was filtrated and concentrated under reduced pressure. To the residue were added $CHCl_3$ (685 μL) and PSA (300 μL). After the stirring at ambient temperature for 14 h, the mixture was purified by silica gel chromatography (NH-silica gel, 50% to 100% EtOAc in hexane and silica gel, $CHCl_3$ to 6% 2 M NH_3/MeOH in $CHCl_3$) to give the desired product.

The product was determined by ESI-MS or APCI-MS.

Example 275-352

To a suspension of 1-cyclohexyl-3-methylpolystyrene-carbodiimide (150 μL) in $CHCl_3$ (400 μL) were added *N*-(*cis*-4-amino-cyclohexyl)-2,*N'*,*N'*-trimethyl-pyrimidine-4,6-diamine obtained in step C of example 6 (30 μmol) in $CHCl_3$ (200 μL) and carboxylic acid (60 μmol) in $CHCl_3$ (200 μL) at ambient temperature. After stirring at the same temperature for 13 h, the mixture was filtrated through NH-silica gel. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel chromatography (silica gel, $CHCl_3$ to 6% 2 M NH_3/MeOH in $CHCl_3$) to give the desired product. The product was determined by ESI-MS or APCI-MS.

Example 353-410

To a solution of half the weight of amide product obtained in example 197-274 in THF (200 μl) was added 1 M borane-THF complex in THF (300 μl). The mixture was stirred at 80 °C for 1 h, and concentrated under reduced pressure. To the residue were added 1 M aqueous HCl (300 μl) and THF (200 μl). The mixture was stirred at 80 °C for 1 h and concentrated under reduced pressure. To the residue was partitioned between $CHCl_3$ and 2 M aqueous sodium hydroxide. The aqueous layer was extracted with $CHCl_3$ (300 μL, twice) and EtOAc (300 μL). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure, and purified by silica gel chromatography (silica gel, 33% EtOAc in hexane to 6% 2 M NH_3/MeOH in $CHCl_3$) to give the desired product. The product was determined by ESI-MS or APCI-MS.

Example 411-451

To a solution of *N*-(*cis*-4-amino-cyclohexyl)-2,*N'*,*N'*-trimethyl-pyrimidine-4,6-diamine obtained in step C of example 6 (30 μmol) in DMSO (300 μL) was added isocyanate or isothiocyanate (60 μmol) in DMSO (200 μL) at ambient temperature. The

mixture was stirred at the same temperature for 12 h and filtrated through a SCX. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel chromatography (silica gel, 50% EtOAc in hexane to 6% 2 M NH_3/MeOH in $CHCl_3$) to give the desired product. The product was determined by ESI-MS or APCI-MS.

Example 452-522

To a suspension of poly(4-vinylpyridine) (75 μL) in $CHCl_3$ (200 μL) were added *N*-(*cis*-4-amino-cyclohexyl)-2,*N'*,*N'*-trimethyl-pyrimidine-4,6-diamine obtained in step C of example 6 (30 μmol) in $CHCl_3$ (200 μL) and chloroformate or sulfonylchloride (60 μmol) in $CHCl_3$ (200 μL) at ambient temperature. After stirring at the same temperature for 14 h, the mixture was filtrated and concentrated under reduced pressure. To the residue were added $CHCl_3$ (685 μL) and PSA (300 μL). After the stirring at ambient temperature for 14 h, the mixture was purified by silica gel chromatography (NH-silica gel, 50% to 100% EtOAc in hexane and silica gel, 33% EtOAc in hexane to 6% 2 M NH_3/MeOH in $CHCl_3$) to give the desired product. The product was determined by ESI-MS or APCI-MS.

Ex. No.	compound name	MS	class
197	2-[(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)amino]-2-oxo- 1-phenylethyl acetate	426 (M + H)	3
198	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-9,10-dioxo-9,10-dihydroanthracene-2-carboxamide	484 (M + H)	3
199	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)acetamide	292 (M + H)	3
200	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)benzamide	354 (M + H)	2
201	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)biphenyl-4-carboxamide	430 (M + H)	3
202	4-tert-butyl-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)benzamide	410 (M + H)	3
203	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-1-benzothiophene-2-carboxamide	409 (M)	3
204	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-{4-[(phenylmethyl)oxy]phenyl}-acetamide	474 (M + H)	3
205	4-bromo-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)benzamide	432 (M + H)	3
206	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-[(phenylmethyl)oxy]acetamide	398 (M + H)	3
207	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2,1,3-benzoxadiazole-5-carboxamide	396 (M + H)	3
208	4-chloro-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)benzamide	388 (M + H)	2
209	2-[(4-chlorophenyl)oxy]-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)acetamide	418 (M + H)	3
210	(2E)-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-3-phenylprop-2-enamide	380 (M + H)	3
211	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)cyclopropanecarboxamide	318 (M + H)	3
212	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)cyclohexanecarboxamide	360 (M + H)	3
213	2-(4-chlorophenyl)-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)acetamide	402 (M + H)	3
214	1-(4-chlorophenyl)-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-cyclopentanecarboxamide	456 (M + H)	1
215	3-(2-chloro-6-fluorophenyl)-N-(cis-4-{ [6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-5-methylisoxazole-4-carboxamide	487 (M + H)	1

Ex. No.	compound name	MS	class
216	4-[(4-chlorophenyl)sulfonyl]-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-3-methylthiophene-2-carboxamide	548 (M + H)	3
217	4-(dimethylamino)-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)benzamide	397 (M + H)	3
218	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-3,4-difluorobenzamide	390 (M + H)	1
219	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-3,4-bis(methyloxy)benzamide	414 (M + H)	3
220	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-4-(ethyloxy)benzamide	398 (M + H)	3
221	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-4-fluorobenzamide	372 (M + H)	3
222	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)furan-2-carboxamide	344 (M + H)	3
223	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)isoxazole-5-carboxamide	345 (M + H)	3
224	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-iodobenzamide	480 (M + H)	3
225	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)morpholine-4-carboxamide	363 (M + H)	3
226	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-(methylthio)pyridine-3-carboxamide	401 (M + H)	3
227	methyl 4-{[(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)amino]carbonyl}benzoate	412 (M + H)	3
228	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-5-methyl-2-phenyl-2H-1,2,3-triazole-4-carboxamide	435 (M + H)	3
229	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-4-methyl-1,2,3-thiadiazole-5-carboxamide	376 (M + H)	3
230	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-(4-methoxyphenoxy)-5-nitrobenzamide	521 (M + H)	2
231	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)naphthalene-2-carboxamide	404 (M + H)	3
232	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-3-nitrobenzamide	399 (M + H)	3
233	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-1-(4-nitrophenyl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide	533 (M + H)	3
234	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-(phenyloxy)acetamide	384 (M + H)	3
235	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-phenylacetamide	368 (M + H)	3

Ex. No.	compound name	MS	class
236	(2R)-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-phenylcyclopropanecarboxamide	394 (M + H)	3
237	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-1,3-benzodioxole-5-carboxamide	398 (M + H)	3
238	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-1-phenyl-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide	488 (M + H)	3
239	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-[(2-nitrophenyl)oxy]acetamide	429 (M + H)	3
240	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)quinoxaline-2-carboxamide	406 (M + H)	3
241	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-3-(trifluoromethyl)benzamide	422 (M + H)	3
242	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-4-methylbenzamide	368 (M + H)	3
243	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)thiophene-2-carboxamide	360 (M + H)	3
244	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-[(pentafluorophenyl)oxy]acetamide	474 (M + H)	3
245	2-[3,4-bis(methyloxy)phenyl]-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)acetamide	428 (M + H)	3
246	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-(phenylthio)acetamide	400 (M + H)	3
247	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-9-oxo-9H-fluorene-4-carboxamide	456 (M + H)	3
248	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-4-[(trifluoromethyl)oxy]benzamide	438 (M + H)	3
249	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-4-fluoro-2-(trifluoromethyl)benzamide	440 (M + H)	3
250	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-(4-fluorophenyl)acetamide	386 (M + H)	3
251	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-4-(heptyloxy)benzamide	468 (M + H)	3
252	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-4-pentylbenzamide	424 (M + H)	3
253	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)cyclopentanecarboxamide	346 (M + H)	3
254	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-4-nonylbenzamide	480 (M + H)	3
255	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-{[4-(1,1-dimethylethyl)phenyl]-oxy}acetamide	440 (M + H)	3

Ex. No.	compound name	MS	class
256	3-chloro-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-4-fluorobenzamide	406 (M + H)	1
257	2-cyclopentyl-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)acetamide	360 (M + H)	3
258	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-3-phenylpropanamide	382 (M + H)	3
259	4-cyano-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)benzamide	379 (M + H)	3
260	N-[4-(6-dimethylamino-2-methyl-pyrimidin-4-ylamino)-cyclohexyl]-2-(naphthalene-1-sulfonylamino)-3-phenyl-propionamide	587 (M + H)	3
261	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-4-[(trifluoromethyl)thio]benzamide	454 (M + H)	3
262	(2E)-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-3-[3-(trifluoromethyl)phenyl]prop-2-enamide	448 (M + H)	3
263	(2E)-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-3-(4-nitrophenyl)prop-2-enamide	425 (M + H)	3
264	2-(2-bromophenyl)-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)acetamide	446 (M + H)	3
265	(2E)-3-(2-chlorophenyl)-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)prop-2-enamide	414 (M + H)	3
266	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-(phenylthio)pyridine-3-carboxamide	463 (M + H)	3
267	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-3-(1,1-dimethylethyl)-1-(phenylmethyl)-1H-pyrazole-5-carboxamide	490 (M + H)	3
268	2-[(4-chlorophenyl)oxy]-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-methylpropanamide	446 (M + H)	3
269	(2E)-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-3-{4-[(trifluoromethyl)oxy]phenyl}prop-2-enamide	464 (M + H)	3
270	1-[(2,4-dichlorophenyl)methyl]-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-3-(1,1-dimethylethyl)-1H-pyrazole-5-carboxamide	558 (M + H)	3
271	6-chloro-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2H-chromene-3-carboxamide	442 (M + H)	3
272	5-chloro-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-1-methyl-1H-pyrazole-4-carboxamide	392 (M + H)	3
273	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-[(4-methyl-2-oxo-2H-chromen-8-yl)oxy]acetamide	466 (M + H)	3

Ex. No.	compound name	MS	class
274	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)acetamide	437 (M+H)	3
275	2-[(4-acetylphenyl)oxy]-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)acetamide	426 (M+H)	3
276	N-((1S)-2-{[(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)amino]carbonyl}cyclohexyl)benzamide	479 (M+H)	3
277	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-1-{[4-(1,1-dimethylethyl)phenyl]sulfonyl}prolinamide	543 (M+H)	3
278	2-cyclohex-1-en-1-yl-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)acetamide	372 (M+H)	3
279	2-cyclohexyl-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)acetamide	374 (M+H)	3
280	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-[(4-methylpyrimidin-2-yl)thio]acetamide	416 (M+H)	3
281	3-[(4-chlorophenyl)sulfonyl]-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)butanamide	494 (M+H)	3
282	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-5-oxo-1-(2-thienylmethyl)pyrrolidine-3-carboxamide	457 (M+H)	3
283	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2,5-dimethyl-1-(2-thienylmethyl)-1H-pyrrole-3-carboxamide	467 (M+H)	3
284	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-(2-fluorobiphenyl-4-yl)propanamide	476 (M+H)	3
285	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-5-iodo-2-furamide	470 (M+H)	3
286	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-[4-(1-oxo-1,3-dihydro-2H-isoindol-2-yl)phenyl]propanamide	513 (M+H)	3
287	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-(2-iodophenyl)acetamide	494 (M+H)	3
288	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-5-(4-methylphenyl)thiophene-3-carboxamide	450 (M+H)	3
289	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-(5-methyl-2-phenyl-1,3-thiazol-4-yl)acetamide	465 (M+H)	3
290	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-[6-(methyloxy)-3-oxo-2,3-dihydro-1H-inden-1-yl]acetamide	452 (M+H)	3
291	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-[7-(methyloxy)-2-oxo-2H-chromen-4-yl]acetamide	466 (M+H)	3

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292	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-4-[4-(methylsulfonyl)phenyl]-4-oxobutanamide	488 (M + H)	3
293	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-5-(methyloxy)-1H-indole-2-carboxamide	423 (M + H)	3
294	N-(2,4-difluorophenyl)-2-{2-[(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)amino]-2-oxoethyl}benzamide	523 (M + H)	3
295	2-(2-{[2,5-bis(methyloxy)phenyl]amino}-2-oxoethyl)-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)benzamide	547 (M + H)	3
296	2-{2-[(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)amino]-2-oxoethyl}-N-[4-(1-methylethyl)phenyl]benzamide	529 (M + H)	3
297	2-{2-[(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)amino]-2-oxoethyl}-N-{4-[(trifluoromethyl)oxy]phenyl}benzamide	571 (M + H)	3
298	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-4-(4-nitrophenyl)butanamide	441 (M + H)	3
299	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-3-oxo-2,3-dihydro-1H-indene-1-carboxamide	408 (M + H)	3
300	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-[4-(phenyloxy)phenyl]acetamide	460 (M + H)	3
301	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-11-phenylundecanamide	494 (M + H)	3
302	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-(pyridin-4-ylthio)acetamide	401 (M + H)	3
303	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-N^2-phenylglycinamide	383 (M + H)	3
304	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-[(4-fluorophenyl)carbonyl]benzamide	476 (M + H)	3
305	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-(2-phenylethyl)benzamide	458 (M + H)	3
306	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-(ethylthio)-2,2-diphenylacetamide	504 (M + H)	1
307	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-4'-(trifluoromethyl)biphenyl-2-carboxamide	498 (M + H)	3
308	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-7-nitro-9H-fluorene-4-carboxamide	487 (M + H)	3
309	(2S)-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-[3-(phenylcarbonyl)phenyl]propanamide	486 (M + H)	3

Ex. No.	compound name	MS	class
310	2-[(4-chlorophenyl)thio]-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-4-(4-methylphenyl)-4-oxobutanamide	566 (M + H)	3
311	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-4-(4-fluorophenyl)-2-[(4-methylphenyl)thio]-4-oxobutanamide	550 (M + H)	3
312	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-[4-(2-thienylcarbonyl)phenyl]-propanamide	492 (M + H)	3
313	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-{4-[(trifluoromethyl)oxy]phenyl}-acetamide	452 (M + H)	3
314	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-4,4,4-trifluoro-3-methylbutanamide	388 (M + H)	3
315	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-{4-[(trifluoromethyl)thio]phenyl}-acetamide	468 (M + H)	3
316	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-5-(2-thienyl)-pentanamide	416 (M + H)	3
317	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-N^2-[(4-methylphenyl)sulfonyl]-glycinamide	461 (M + H)	3
318	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-{5-[(phenylmethyl)oxy]-1H-indol-3-yl}acetamide	513 (M + H)	3
319	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-N'-(3-methylphenyl)benzene-1,2-dicarboxamide	487 (M + H)	3
320	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-3-methyl-4-oxo-2-phenyl-4H-chromene-8-carboxamide	512 (M + H)	3
321	phenylmethyl 3-[(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)amino]-3-oxo-2-phenylpropanoate	502 (M + H)	3
322	2-{[3,5-bis(trifluoromethyl)phenyl]carbonyl}-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-benzamide	594 (M + H)	3
323	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-[(3-methyl-1-benzothien-2-yl)carbonyl]benzamide	528 (M + H)	3
324	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-9-oxo-9H-fluorene-2-carboxamide	456 (M + H)	3
325	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)biphenyl-2-carboxamide	430 (M + H)	3

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326	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-4-(phenyloxy)benzamide	446 (M + H)	3
327	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-9H-xanthene-9-carboxamide	458 (M + H)	3
328	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-N'-[(1S)-1-phenylethyl]benzene-1,2-dicarboxamide	501 (M + H)	3
329	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-4-[(phenylmethyl)oxy]benzamide	460 (M + H)	3
330	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-[(4-methylphenyl)carbonyl]benzamide	472 (M + H)	3
331	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-[(phenyloxy)methyl]benzamide	460 (M + H)	3
332	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-N'-naphthalen-1-ylbenzene-1,2-dicarboxamide	523 (M + H)	3
333	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)anthracene-2-carboxamide	454 (M + H)	3
334	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-4'-heptylbiphenyl-4-carboxamide	528 (M + H)	3
335	2-[4-(4-chlorophenyl)-2-phenyl-1,3-thiazol-5-yl]-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}-cyclohexyl)acetamide	561 (M + H)	3
336	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-[(phenylmethyl)thio]acetamide	414 (M + H)	3
337	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-4-phenylbutanamide	396 (M + H)	3
338	2-(1-benzothien-3-yl)-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)acetamide	424 (M + H)	3
339	2-(2,3-dihydro-1H-inden-2-yl)-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)acetamide	408 (M + H)	3
340	4-[3,4-bis(methyloxy)phenyl]-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)butanamide	456 (M + H)	3
341	4-(2,3-dihydro-1,4-benzodioxin-6-yl)-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-butanamide	454 (M + H)	3
342	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-1-[(4-methylphenyl)sulfonyl]-1H-pyrrole-3-carboxamide	497 (M + H)	3
343	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-4-(methylsulfonyl)benzamide	432 (M + H)	3
344	5-acetyl-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)thiophene-2-carboxamide	402 (M + H)	3

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345	3-chloro-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-4-[(1-methylethyl)sulfonyl]-5-(methylthio)thiophene-2-carboxamide	546 (M + H)	3
346	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-5-(methylsulfonyl)thiophene-2-carboxamide	438 (M + H)	3
347	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-4-(1,3-oxazol-5-yl)benzamide	421 (M + H)	3
348	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-1-(phenylsulfonyl)-1H-indole-3-carboxamide	533 (M + H)	3
349	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-oxo-2-phenylacetamide	382 (M + H)	3
350	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-oxo-2-(2,4,6-trimethylphenyl)acetamide	424 (M + H)	3
351	(2R,5S)-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-5-phenyl-2-(phenylcarbonyl)cyclohexanecarboxamide	540 (M + H)	3
352	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-(9H-fluoren-9-ylidene)acetamide	454 (M + H)	3
353	2-{[(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)amino]methyl}anthracene-9,10-dione	470 (M + H)	3
354	N,N,2-trimethyl-N'-{cis-4-[(phenylmethyl)amino]cyclohexyl}pyrimidine-4,6-diamine	340 (M + H)	3
355	N'-{cis-4-[(biphenyl-4-ylmethyl)amino]cyclohexyl}-N,N,2-trimethylpyrimidine-4,6-diamine	416 (M + H)	3
356	N'-[cis-4-({[4-(1,1-dimethylethyl)phenyl]methyl}amino)-cyclohexyl]-N,N,2-trimethylpyrimidine-4,6-diamine	396 (M + H)	3
357	N'-{cis-4-[(1-benzothien-2-ylmethyl)amino]cyclohexyl}-N,N,2-trimethylpyrimidine-4,6-diamine	396 (M + H)	3
358	N'-(cis-4-{[(4-bromophenyl)methyl]amino}cyclohexyl)-N,N,2-trimethylpyrimidine-4,6-diamine	418 (M + H)	3
359	N,N,2-trimethyl-N'-[cis-4-({2-[(phenylmethyl)oxy]ethyl}amino)cyclohexyl]pyrimidine-4,6-diamine	384 (M + H)	3
360	N'-(cis-4-{[(4-chlorophenyl)methyl]amino}cyclohexyl)-N,N,2-trimethylpyrimidine-4,6-diamine	374 (M + H)	3
361	N'-[cis-4-({2-[(4-chlorophenyl)oxy]ethyl}amino)cyclohexyl]-N,N,2-trimethylpyrimidine-4,6-diamine	404 (M + H)	3
362	N'-{cis-4-[(cyclopropylmethyl)amino]cyclohexyl}-N,N,2-trimethylpyrimidine-4,6-diamine	304 (M + H)	3
363	N'-{cis-4-[(cyclohexylmethyl)amino]cyclohexyl}-N,N,2-trimethylpyrimidine-4,6-diamine	346 (M + H)	3

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364	N'-(cis-4-{[2-(4-chlorophenyl)ethyl]amino}cyclohexyl)-N,N,2-trimethylpyrimidine-4,6-diamine	388 (M + H)	3
365	N'-[cis-4-({[1-(4-chlorophenyl)cyclopentyl]methyl}-amino)cyclohexyl]-N,N,2-trimethylpyrimidine-4,6-diamine	442 (M + H)	3
366	N'-[cis-4-({[3-(2-chloro-6-fluorophenyl)-5-methylisoxazol-4-yl]methyl}amino)cyclohexyl]-N,N,2-trimethylpyrimidine-4,6-diamine	473 (M + H)	3
367	N'-{cis-4-[({4-[(4-chlorophenyl)sulfonyl]-3-methyl-2-thienyl}methyl)amino]cyclohexyl}-N,N,2-trimethylpyrimidine-4,6-diamine	534 (M + H)	3
368	N'-[cis-4-({[4-(dimethylamino)phenyl]methyl}amino)-cyclohexyl]-N,N,2-trimethylpyrimidine-4,6-diamine	383 (M + H)	3
369	N'-(cis-4-{[(3,4-difluorophenyl)methyl]amino}cyclohexyl)-N,N,2-trimethylpyrimidine-4,6-diamine	376 (M + H)	3
370	N'-[cis-4-({[3,4-bis(methyloxy)phenyl]methyl}amino)-cyclohexyl]-N,N,2-trimethylpyrimidine-4,6-diamine	400 (M + H)	3
371	N'-[cis-4-({[4-(ethyloxy)phenyl]methyl}amino)cyclohexyl]-N,N,2-trimethylpyrimidine-4,6-diamine	384 (M + H)	3
372	N'-(cis-4-{[(4-fluorophenyl)methyl]amino}cyclohexyl)-N,N,2-trimethylpyrimidine-4,6-diamine	358 (M + H)	3
373	N'-{cis-4-[(furan-2-ylmethyl)amino]cyclohexyl}-N,N,2-trimethylpyrimidine-4,6-diamine	330 (M + H)	3
374	N'-{cis-4-[(isoxazol-5-ylmethyl)amino]cyclohexyl}-N,N,2-trimethylpyrimidine-4,6-diamine	331 (M + H)	3
375	N'-(cis-4-{[(2-iodophenyl)methyl]amino}cyclohexyl)-N,N,2-trimethylpyrimidine-4,6-diamine	466 (M + H)	3
376	N,N,2-trimethyl-N'-(cis-4-{[(5-methyl-2-phenyl-2H-1,2,3-triazol-4-yl)methyl]amino}cyclohexyl)pyrimidine-4,6-diamine	421 (M + H)	3
377	N,N,2-trimethyl-N'-(cis-4-{[(2-{[4-(methyloxy)phenyl]oxy}-5-nitrophenyl)methyl]amino}cyclohexyl)pyrimidine-4,6-diamine	507 (M + H)	3
378	N,N,2-trimethyl-N'-{cis-4-[(naphthalen-2-ylmethyl)amino]cyclohexyl}pyrimidine-4,6-diamine	390 (M + H)	3
379	N,N,2-trimethyl-N'-(cis-4-{[(3-nitrophenyl)methyl]amino}cyclohexyl)pyrimidine-4,6-diamine	385 (M + H)	3
380	N,N,2-trimethyl-N'-[cis-4-({[1-(4-nitrophenyl)-5-(trifluoromethyl)-1H-pyrazol-4-yl]methyl}amino)cyclohexyl]-pyrimidine-4,6-diamine	519 (M + H)	3
381	N,N,2-trimethyl-N'-(cis-4-{[2-(phenyloxy)ethyl]amino}cyclohexyl)pyrimidine-4,6-diamine	370 (M + H)	3
382	N,N,2-trimethyl-N'-{cis-4-[(2-phenylethyl)amino]cyclohexyl}pyrimidine-4,6-diamine	354 (M + H)	3
383	N,N,2-trimethyl-N'-[cis-4-({[(2R)-2-phenylcyclopropyl]methyl}amino)cyclohexyl]pyrimidine-4,6-diamine	380 (M + H)	3

Ex. No.	compound name	MS	class
384	N,N,2-trimethyl-N'-[cis-4-({[1-phenyl-5-(trifluoromethyl)-1H-pyrazol-4-yl]methyl}amino)cyclohexyl]pyrimidine-4,6-diamine	474 (M + H)	3
385	N,N,2-trimethyl-N'-[cis-4-({2-[(2-nitrophenyl)oxy]ethyl}amino)cyclohexyl]pyrimidine-4,6-diamine	415 (M + H)	3
386	N,N,2-trimethyl-N'-[cis-4-({[3-(trifluoromethyl)phenyl]methyl}amino)cyclohexyl]pyrimidine-4,6-diamine	408 (M + H)	3
387	N,N,2-trimethyl-N'-(cis-4-{[(4-methylphenyl)methyl]amino}cyclohexyl)pyrimidine-4,6-diamine	354 (M + H)	3
388	N,N,2-trimethyl-N'-{cis-4-[(2-thienylmethyl)amino]cyclohexyl}pyrimidine-4,6-diamine	346 (M + H)	3
389	N,N,2-trimethyl-N'-[cis-4-({2-[(pentafluorophenyl)oxy]ethyl}amino)cyclohexyl]pyrimidine-4,6-diamine	460 (M + H)	3
390	N'-[cis-4-({2-[3,4-bis(methyloxy)phenyl]ethyl}amino)-cyclohexyl]-N,N,2-trimethylpyrimidine-4,6-diamine	414 (M + H)	3
391	N,N,2-trimethyl-N'-(cis-4-{[2-(phenylthio)ethyl]amino}cyclohexyl)pyrimidine-4,6-diamine	386 (M + H)	3
392	4-{[(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)amino]methyl}-9H-fluoren-9-one	442 (M + H)	3
393	N,N,2-trimethyl-N'-{cis-4-[({4-[(trifluoromethyl)oxy]phenyl}methyl)amino]cyclohexyl}-pyrimidine-4,6-diamine	424 (M + H)	3
394	N'-[cis-4-({[4-fluoro-2-(trifluoromethyl)phenyl]methyl}amino)cyclohexyl]-N,N,2-trimethylpyrimidine-4,6-diamine	426 (M + H)	3
395	N'-(cis-4-{[2-(4-fluorophenyl)ethyl]amino}cyclohexyl)-N,N,2-trimethylpyrimidine-4,6-diamine	372 (M + H)	3
396	N'-[cis-4-({[4-(heptyloxy)phenyl]methyl}amino)cyclohexyl]-N,N,2-trimethylpyrimidine-4,6-diamine	454 (M + H)	3
397	N,N,2-trimethyl-N'-(cis-4-{[(4-pentylphenyl)methyl]amino}cyclohexyl)pyrimidine-4,6-diamine	410 (M + H)	3
398	N'-{cis-4-[(cyclopentylmethyl)amino]cyclohexyl}-N,N,2-trimethylpyrimidine-4,6-diamine	332 (M + H)	3
399	N,N,2-trimethyl-N'-(cis-4-{[(4-nonylphenyl)methyl]amino}cyclohexyl)pyrimidine-4,6-diamine	466 (M + H)	3
400	N'-{cis-4-[(2-{[4-(1,1-dimethylethyl)phenyl]oxy}ethyl)amino]cyclohexyl}-N,N,2-trimethylpyrimidine-4,6-diamine	426 (M + H)	3
401	N'-(cis-4-{[(3-chloro-4-fluorophenyl)methyl]amino}cyclohexyl)-N,N,2-trimethylpyrimidine-4,6-diamine	392 (M + H)	3
402	N'-{cis-4-[(2-cyclopentylethyl)amino]cyclohexyl}-N,N,2-trimethylpyrimidine-4,6-diamine	346 (M + H)	3

Ex. No.	compound name	MS	class
403	N,N,2-trimethyl-N'-{cis-4-[(3-phenylpropyl)amino]cyclohexyl}pyrimidine-4,6-diamine	368 (M + H)	3
404	N-[(1S)-2-[(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)amino]-1-(phenylmethyl)ethyl]naphthalene-1-sulfonamide	573 (M + H)	3
405	N,N,2-trimethyl-N'-{cis-4-[({4-[(trifluoromethyl)thio]phenyl}methyl)amino]cyclohexyl}-pyrimidine-4,6-diamine	440 (M + H)	3
406	N'-(cis-4-{[2-(2-bromophenyl)ethyl]amino}cyclohexyl)-N,N,2-trimethylpyrimidine-4,6-diamine	432 (M + H)	3
407	N'-[cis-4-({[3-(1,1-dimethylethyl)-1-(phenylmethyl)-1H-pyrazol-5-yl]methyl}amino)cyclohexyl]-N,N,2-trimethylpyrimidine-4,6-diamine	476 (M + H)	3
408	N'-[cis-4-({2-[(4-chlorophenyl)oxy]-2-methylpropyl}-amino)cyclohexyl]-N,N,2-trimethylpyrimidine-4,6-diamine	432 (M + H)	3
409	N'-[cis-4-({[1-[(2,4-dichlorophenyl)methyl]-3-(1,1-dimethylethyl)-1H-pyrazol-5-yl]methyl}amino)cyclohexyl]-N,N,2-trimethylpyrimidine-4,6-diamine	544 (M + H)	3
410	N'-(cis-4-{[(5-chloro-1-methyl-1H-pyrazol-4-yl)methyl]amino}cyclohexyl)-N,N,2-trimethylpyrimidine-4,6-diamine	378 (M + H)	3
411	methyl N-{[(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)amino]carbonyl}phenylalaninate	455 (M + H)	3
412	N-[(2-chlorophenyl)methyl]-N'-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)urea	417 (M + H)	3
413	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-N'-[(4-fluorophenyl)methyl]urea	401 (M + H)	3
414	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-N'-(diphenylmethyl)urea	459 (M + H)	3
415	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-N'-[1-(1-naphthyl)ethyl]urea	447 (M + H)	1
416	N-(4-bromo-2,6-dimethylphenyl)-N'-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)urea	475 (M + H)	1
417	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-N'-(2,4,6-trimethylphenyl)urea	411 (M + H)	3
418	N-(4-chloro-2-methylphenyl)-N'-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)urea	417 (M + H)	3
419	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-N'-[2-ethyl-6-(1-methylethyl)phenyl]urea	439 (M + H)	3
420	N-(4-bromo-2-methylphenyl)-N'-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)urea	461 (M + H)	3
421	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-N'-(2-ethyl-6-methylphenyl)urea	411 (M + H)	3

Ex. No.	compound name	MS	class
422	N-(2-tert-butyl-6-methylphenyl)-N'-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)urea	439 (M + H)	2
423	N-[2,6-dibromo-4-(1-methylethyl)phenyl]-N'-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)urea	567 (M + H)	3
424	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-N'-{2-[(trifluoromethyl)oxy]phenyl}urea	453 (M + H)	3
425	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-N'-(3,4,5-trimethoxyphenyl)urea	459 (M + H)	1
426	N-(5-chloro-2,4-dimethoxyphenyl)-N'-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)urea	463 (M + H)	2
427	N-[3-(cyclopentyloxy)-4-(methyloxy)phenyl]-N'-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)urea	483 (M + H)	3
428	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-N'-[2-(ethyloxy)phenyl]urea	413 (M + H)	3
429	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-N'-(2,4,6-tribromophenyl)urea	603 (M + H)	1
430	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-N'-(2,4,6-trichlorophenyl)urea	471 (M + H)	3
431	N-(2,4-dibromo-6-fluorophenyl)-N'-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)urea	543 (M + H)	3
432	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-N'-naphthalen-1-ylurea	419 (M + H)	3
433	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-N'-(3-methyl-5-phenylisoxazol-4-yl)urea	450 (M + H)	3
434	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-N'-(2,2-diphenylethyl)thiourea	489 (M + H)	3
435	N-[4-bromo-2-(trifluoromethyl)phenyl]-N'-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}-cyclohexyl)thiourea	532 (M + H)	3
436	N-(4-bromo-2,6-dimethylphenyl)-N'-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)thiourea	492 (M + H)	2
437	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-N'-mesitylthiourea	427 (M + H)	2
438	N-(2,6-diethylphenyl)-N'-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)thiourea	441 (M + H)	2
439	N-(2,4-dichloro-6-methylphenyl)-N'-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)thiourea	468 (M + H)	2
440	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-N'-[4-(dimethylamino)-1-naphthyl]thiourea	478 (M + H)	3
441	N-{4-bromo-2-[(trifluoromethyl)oxy]phenyl}-N'-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}-cyclohexyl)thiourea	548 (M + H)	3

Ex. No.	compound name	MS	class
442	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-N'-(3,4,5-trimethoxyphenyl)thiourea	475 (M + H)	1
443	N-(5-chloro-2,4-dimethoxyphenyl)-N'-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}-cyclohexyl)thiourea	480 (M + H)	2
444	N-[2,4-bis(methyloxy)phenyl]-N'-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)thiourea	445 (M + H)	3
445	N-[3,4-bis(methyloxy)phenyl]-N'-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)thiourea	445 (M + H)	3
446	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-N'-[2-(ethyloxy)phenyl]thiourea	429 (M + H)	3
447	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-N'-(2,4,6-tribromophenyl)thiourea	621 (M + H)	1
448	N-(2,4-dibromo-6-fluorophenyl)-N'-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)thiourea	559 (M + H)	3
449	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-N'-(4-iodophenyl)thiourea	511 (M + H)	3
450	N-(4-cyanophenyl)-N'-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)thiourea	410 (M + H)	3
451	methyl 3-({[(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)amino]carbonothioyl}amino)-4-methylthiophene-2-carboxylate	463 (M + H)	3
452	2,2-dimethylpropyl (cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)carbamate	364 (M + H)	3
453	[4,5-bis(methyloxy)-2-nitrophenyl]methyl (cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}-cyclohexyl)carbamate	489 (M + H)	3
454	3-(trifluoromethyl)phenyl (cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)carbamate	438 (M + H)	3
455	4-bromophenyl (cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)carbamate	448 (M + H)	3
456	2-(methyloxy)phenyl (cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)carbamate	400 (M + H)	3
457	2-(methyloxy)ethyl (cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)carbamate	352 (M + H)	3
458	octyl (cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)carbamate	406 (M + H)	3
459	ethyl (cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)carbamate	322 (M + H)	3
460	(4-nitrophenyl)methyl (cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)carbamate	429 (M + H)	3
461	naphthalen-2-yl (cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)carbamate	420 (M + H)	3

Ex. No.	compound name	MS	class
462	prop-2-en-1-yl (cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)carbamate	334 (M + H)	3
463	phenylmethyl (cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)carbamate	384 (M + H)	3
464	phenyl (cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)carbamate	370 (M + H)	3
465	(2S,5R)-5-methyl-2-(1-methylethyl)cyclohexyl (cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}-cyclohexyl)carbamate	432 (M + H)	3
466	4-methylphenyl (cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)carbamate	384 (M + H)	3
467	methyl (cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)carbamate	308 (M + H)	3
468	(2-chlorophenyl)methyl (cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)carbamate	418 (M + H)	3
469	9H-fluoren-9-ylmethyl (cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)carbamate	472 (M + H)	3
470	2,2,2-trichloroethyl (cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)carbamate	424 (M + H)	3
471	(E)-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-phenylethenesulfonamide	416 (M + H)	3
472	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-1-[3-(trifluoromethyl)phenyl]-methanesulfonamide	472 (M + H)	3
473	1-(3,4-dichlorophenyl)-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)methanesulfonamide	472 (M + H)	3
474	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-1-(4-fluorophenyl)methanesulfonamide	422 (M + H)	3
475	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-1-(2-nitrophenyl)methanesulfonamide	449 (M + H)	3
476	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-1-phenylmethanesulfonamide	404 (M + H)	3
477	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-naphthalen-1-ylethanesulfonamide	468 (M + H)	3
478	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)methanesulfonamide	328 (M + H)	3
479	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)propane-2-sulfonamide	356 (M + H)	3
480	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)octane-1-sulfonamide	426 (M + H)	3
481	methyl 2-{[(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)amino]sulfonyl}benzoate	448 (M + H)	3

Ex. No.	compound name	MS	class
482	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-4-ethenylbenzenesulfonamide	416 (M + H)	3
483	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-3-(trifluoromethyl)benzenesulfonamide	458 (M + H)	3
484	4-acetyl-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)benzenesulfonamide	432 (M + H)	3
485	3-chloro-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-4-methylbenzenesulfonamide	438 (M + H)	3
486	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2,4,6-trimethylbenzenesulfonamide	432 (M + H)	3
487	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-4-propylbenzenesulfonamide	432 (M + H)	3
488	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-4-(1,1-dimethylpropyl)benzenesulfonamide	460 (M + H)	3
489	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)biphenyl-4-sulfonamide	466 (M + H)	3
490	5-(dimethylamino)-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)naphthalene-1-sulfonamide	483 (M + H)	3
491	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-[(trifluoromethyl)oxy]-benzenesulfonamide	474 (M + H)	3
492	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-3-[(trifluoromethyl)oxy]-benzenesulfonamide	474 (M + H)	3
493	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-3-(methyloxy)benzenesulfonamide	420 (M + H)	3
494	4-(butyloxy)-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)benzenesulfonamide	462 (M + H)	3
495	3,5-dichloro-4-[(2-chloro-4-nitrophenyl)oxy]-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)benzenesulfonamide	629 (M + H)	3
496	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-4-(phenyloxy)benzenesulfonamide	482 (M + H)	3
497	4-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)benzenesulfonamide	585 (M + H)	3
498	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-4-(methylsulfonyl)benzenesulfonamide	468 (M + H)	3
499	3-cyano-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)benzenesulfonamide	415 (M + H)	3
500	3-bromo-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)benzenesulfonamide	468 (M + H)	3

Ex. No.	compound name	MS	class
501	4-bromo-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-[(trifluoromethyl)oxy]-benzenesulfonamide	552 (M + H)	3
502	3,4-dichloro-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)benzenesulfonamide	458 (M + H)	3
503	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-3-fluorobenzenesulfonamide	408 (M + H)	3
504	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-3-nitrobenzenesulfonamide	435 (M + H)	3
505	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)naphthalene-1-sulfonamide	440 (M + H)	3
506	ethyl 4-{[(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)amino]sulfonyl}-2-methyl-1,5-diphenyl-1H-pyrrole-3-carboxylate	617 (M + H)	3
507	methyl 5-{[(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)amino]sulfonyl}-1-methyl-1H-pyrrole-2-carboxylate	451 (M + H)	3
508	methyl 5-{[(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)amino]sulfonyl}-2-methylfuran-3-carboxylate	452 (M + H)	3
509	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline-7-sulfonamide	541 (M + H)	3
510	5-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]methyl}-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)thiophene-2-sulfonamide	589 (M + H)	3
511	5-chloro-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-3-methyl-1-benzothiophene-2-sulfonamide	494 (M + H)	3
512	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-3,5-dimethylisoxazole-4-sulfonamide	409 (M + H)	3
513	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-1,3,5-trimethyl-1H-pyrazole-4-sulfonamide	422 (M + H)	3
514	ethyl 5-(4-chlorophenyl)-4-{[(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)amino]sulfonyl}-2-methyl-1-phenyl-1H-pyrrole-3-carboxylate	651 (M + H)	3
515	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-5-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]thiophene-2-sulfonamide	544 (M + H)	3
516	1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-1H-pyrrole-2-sulfonamide	558 (M + H)	3
517	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-5-isoxazol-3-ylthiophene-2-sulfonamide	463 (M + H)	3

Ex. No.	compound name	MS	class
518	methyl 5-{[(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)amino]sulfonyl}-4-(methyloxy)thiophene-3-carboxylate	484 (M + H)	3
519	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-4-(phenylsulfonyl)thiophene-2-sulfonamide	536 (M + H)	3
520	5-bromo-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)thiophene-2-sulfonamide	474 (M + H)	3
521	7-chloro-N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)-2,1,3-benzoxadiazole-4-sulfonamide	466 (M + H)	3
522	N-(cis-4-{[6-(dimethylamino)-2-methylpyrimidin-4-yl]amino}cyclohexyl)quinoline-8-sulfonamide	441 (M + H)	3

Assay Procedures

ASSAY FOR DETERMINATION OF CONSTITUTIVE ACTIVITY OF NON-ENDOGENOUS GPCRS

Example 523

Intracellular IP_3 Accumulation Assay

On day 1, cells to be tranfected can be plated onto 24 well plates, usually $1x10^5$ cells/well (although his umber can be optimized. On day 2 cells can be transfected by firstly mixing 0.25μg DNA (e.g., pCMV vector or pCMV vector comprising polynucleotide enocoding receptor) in 50 μl serum free DMEM/well and 2 μl lipofectamine in 50 μl serum-free DMEM/well. The solutions are gently mixed and incubated for 15-30 min at room temperature. Cells are washed with 0.5 mL PBS and 400 μl of serum free media is mixed with the transfection media and added to the cells. The cells are then incubated for 3-4 hrs at 37°C/5%CO_2 and then the transfection media is removed and replaced with 1ml/well of regular growth media. On day 3 the cells are labeled with ^{3}H-myo-inositol. Briefly, the media is removed and the cells are washed with 0.5 ml PBS. Then 0.5 mL inositol-free/serum free media (GIBCO BRL) is added/well with 0.25 μCi of ^{3}H-myo-inositol/ well and the cells are incubated for 16-18 hrs o/n at 37°C/5%CO_2 On Day 4 the cells are washed with 0.5 ml PBS and 0.45 ml of assay medium is added containing inositol-free/serum free media 10μM pargyline 10 mM lithium chloride or 0.4 mL of assay medium and 50 μl of 10x ketanserin (ket) to final concentration of 10μM. The cells are then incubated for 30 min at 37°C. The cells are then washed with 0.5 mL PBS and 200 μl of fresh/ice cold stop solution (1M KOH; 18 mM Na-borate; 3.8 mM EDTA) is added/well. The solution is kept on ice for 5-10 min or until cells were lysed and then neutralized by 200 μl of fresh/ice cold neutralization sol. (7.5 % HCL). The lysate is then transferred into 1.5 mL eppendorf tubes and 1 mL of chloroform/methanol (1:2) is added/tube. The solution is vortexed for 15 sec and the upper phase is applied to a Biorad AG1-X8™ anion exchange resin (100-200 mesh). Firstly, the resin is washed with water at 1:1.25 W/V and 0.9 mL of upper phase is loaded onto the

column. The column is washed with 10 mls of 5 mM myo-inositol and 10 mL of 5 mM Na-borate/60mM Na-formate. The inositol tris phosphates are eluted into scintillation vials containing 10 mL of scintillation cocktail with 2 mL of 0.1 M formic acid/ 1 M ammonium formate. The columns are regenerated by washing with 10 ml of 0.1 M formic acid/3M ammonium formate and rinsed twice with H_2O and stored at 4°C in water.

Example 524

High Throughput Functional Screening: FLIPR™

Subsequently, a functional based assay was used to confirm the lead hits, referred to as FLIPR™ (the Fluorometric Imaging Plate Reader) and FDSS6000™ (Functional Drug Screening System). This assay utilized a non-endogenous, constitutively active version of the MCH receptor.

The FLIPR and FDSS assays are able to detect intracellular Ca^{2+} concentration in cells, which can be utilized to assess receptor activation and determine whether a candidate compound is an, for example, antagonist, inverse agonist or agonist to a Gq-coupled receptor. The concentration of free Ca^{2+} in the cytosol of any cell is extremely low, whereas its concentration in the extracellular fluid and endoplasmic reticulum (ER) is very high. Thus, there is a large gradient tending to drive Ca^{2+} into the cytosol across both the plasma membrane and ER. The FLIPR™ and FDSS6000™ systems (Molecular Devices Corporation, HAMAMATSU Photonics K.K.) are designed to perform functional cell-based assays, such as the measurement of intracellular calcium for high-throughput screening. The measurement of fluorescent is associated with calcium release upon activation of the Gq-coupled receptors. Gi or Go coupled receptors are not as easily monitored through the FLIPR™ and FDSS6000™ systems because these G proteins do not couple with calcium signal pathways.

Fluorometric Imaging Plate Reader system was used to allow for rapid, kinetic measurements of intracellular fluorescence in 96 well microplates (or 384 well microplates). Simultaneous measurements of fluorescence in all wells can be made by

FLIPR or FDSS6000™ every second with high sensitivity and precision. These systems are ideal for measuring cell-based functional assays such as monitoring the intracellular calcium fluxes that occur within seconds after activation of the Gq coupled receptor.

Briefly, the cells are seeded into 96 well at $5.5x10^4$ cells/well with complete culture media (Dulbecco's Modified Eagle Medium with 10 % fetal bovine serum, 2 mM L-glutamine, 1 mM sodium pyruvate and 0.5 mg/mL G418, pH 7.4) for the assay next day. On the day of assay, the media is removed and the cells are incubated with 100 µl of loading buffer (4 µM Fluo4-AM in complete culture media containing 2.5 mM Probenicid, 0.5 mg/ml and 0.2% bovine serum albumin) in 5% CO_2 incubator at 37°C for 1 hr. The loading buffer is removed, and the cells are washed with wash buffer (Hank's Balanced Salt Solution containing 2.5 mM Probenicid, 20 mM HEPES, 0.5 mg/mL and 0.2% bovine serum albumin, pH 7.4). One hundred fifty µl of wash buffer containing various concentrations of test compound is added to the cells, and the cells are incubated in 5% CO_2 incubator at 37°C for 30 min. Fifty µl of wash buffer containing various concentration of MCH are added to each well, and transient changes in $[Ca^{2+}]i$ evoked by MCH are monitored using the FLIPR or FDSS in 96 well plates at Ex. 488 nm and Em. 530 nm for 290 second. When antagonist activity of compound is tested, 50 nM of MCH is used.

Use of FLIPR™ and FDSS6000™ can be accomplished by following manufacturer's instruction (Molecular Device Corporation and HAMAMATSU Photonics K.K.).

Representative examples are shown below.

Compound No.	IC_{50} (nM)
Example 7	101
Example 24	26

The results were shown on the tables in the Examples section and the table in the

next page in accordance with the classification as defined below.

Class 1 : The value of percent of control at 10^{-7} M was less than 40% or the value of IC_{50} was less than 50 nM.

Class 2 : The value of percent of control at 10^{-7} M was from 40% to 60% or the value of IC_{50} was from 50 nM to 200 nM.

Class 3 : The value of percent of control at 10^{-7} M was more than 60% or the value of IC_{50} was more than 200 nM.

Ex. No.	class	Ex. No.	class	Ex. No.	class	Ex. No.	class	Ex. No.	class
1	3	17	1	33	2	169	2	185	3
2	2	18	1	34	3	170	1	186	3
3	3	19	3	35	3	171	3	187	2
4	3	20	3	36	3	172	3	188	2
5	1	21	1	37	3	173	3	189	3
6	1	22	3	38	3	174	3	190	3
7	2	23	2	39	2	175	3	191	1
8	1	24	1	40	1	176	3	192	2
9	2	25	2	41	3	177	1	193	1
10	1	26	2	42	3	178	3	194	3
11	1	27	2	43	2	179	1	195	3
12	2	28	3	44	1	180	3	196	3
13	2	29	3	45	2	181	3		
14	1	30	3	46	3	182	3		
15	3	31	2	47	3	183	3		
16	2	32	1	168	3	184	3		

Example 525

Receptor Binding Assay

In addition to the methods described herein, another means for evaluating a test compound is by determining binding affinities to the **MCH** receptor. This type of assay generally requires a radiolabelled ligand to the **MCH** receptor. Absent the use of known ligands for the **MCH** receptor and radiolabels thereof, compounds of Formula (**I**) can be labelled with a radioisotope and used in an assay for evaluating the affinity of a test

compound to the MCH receptor.

A radiolabelled MCH compound of Formula (I) can be used in a screening assay to identify/evaluate compounds. In general terms, a newly synthesized or identified compound (i.e., test compound) can be evaluated for its ability to reduce binding of the "radiolabelled compound of Formula (I)" to the MCH receptor. Accordingly, the ability to compete with the "radio-labelled compound of Formula (I)" or **Radiolabelled MCH Ligand** for the binding to the MCH receptor directly correlates to its binding affinity of the test compound to the MCH receptor.

ASSAY PROTOCOL FOR DETERMINING RECEPTOR BINDING FOR MCH:

A. MCH RECEPTOR PREPARATION

293 cells (human kidney, ATCC), transiently transfected with 10 μg human MCH receptor and 60 μl Lipofectamine (per 15-cm dish), are grown in the dish for 24 hours (75% confluency) with a media change and removed with 10 mL/dish of Hepes-EDTA buffer (20mM Hepes + 1 0 mM EDTA, pH 7.4). The cells are then centrifuged in a Beckman Coulter centrifuge for 20 minutes, 17,000 rpm (JA-25.50 rotor). Subsequently, the pellet is resuspended in 20 mM Hepes + 1 mM EDTA, pH 7.4 and homogenized with a 50- mL Dounce homogenizer and again centrifuged. After removing the supernatant, the pellets can be stored at -8 0°C, until used in binding assay. When used in the assay, membranes are thawed on ice for 20 minutes and then 10 mL of incubation buffer (20 mM Hepes, 1 mM $MgCl_2$, 10O mM NaCl, pH 7.4) added. The membranes are then vortexed to resuspend the crude membrane pellet and homogenized with a Brinkmann PT-310O Polytron homogenizer for 15 seconds at setting 6. The concentration of membrane protein is determined using the BRL Bradford protein assay.

B. BINDING ASSAY

For total binding, a total volume of 50ul of appropriately diluted membranes (diluted in assay buffer containing 50mM Tris HCl (pH 7.4), 10mM $MgCl_2$, and 1mM

EDTA; 5-50ug protein) is added to 96-well polyproylene microtiter plates followed by addition of 100 µl of assay buffer and 50 µl of **Radiolabelled MCH Ligand**. For nonspecific binding, 50 µl of assay buffer is added instead of 100 µl and an additional 50 µl of 10uM cold **MCH** is added before 50 µl of **Radiolabelled MCH Ligand** is added. Plates are then incubated at room temperature for 60-120 minutes. The binding reaction is terminated by filtering assay plates through a Microplate Devices GF/C Unifilter filtration plate with a Brandell 96-well plate harvestor followed by washing with cold 50 mM Tris HCl, pH 7.4 containing 0.9% NaCl. Then, the bottom of the filtration plate are sealed, 50ul of Optiphase Supermix is added to each well, the top of the plates are sealed, and plates are counted in a Trilux MicroBeta scintillation counter. For compound competition studies, instead of adding 100 µl of assay buffer, 100 µl of appropriately diluted test compound is added to appropriate wells followed by addition of 50 µl of **Radiolabelled MCH Ligand.**

C. CALCULATIONS

The test compounds are initially assayed at 1 and 0.1 µM and then at a range of concentrations chosen such that the middle dose would cause about 50% inhibition of a **Radiolabelled MCH Ligand** binding (i.e., IC_{50}). Specific binding in the absence of test compound (B_O) is the difference of total binding (B_T) minus non-specific binding (NSB) and similarly specific binding (in the presence of test compound) (B) is the difference of displacement binding (B_D) minus non-specific binding (NSB). IC_{50} is determined from an inhibition response curve, logit-log plot of % B/B_O vs concentration of test compound.

K_i is calculated by the Cheng and Prustoff transformation:

$$K_i = IC_{50}/(1+[L]/K_D)$$

wherein [L] is the concentration of a **Radiolabelled MCH Ligand** used in the assay and K_D is the dissociation constant of a **Radiolabelled MCH Ligand** determined independently under the same binding conditions.

It is intended that each of the patents, applications, printed publications, and other published documents mentioned or referred to in this specification be herein incorporated by reference in their entirety.

Those skilled in the art will appreciate that numerous changes and modifications may be made to the preferred embodiments of the invention and that such changes and modifications may be made without departing from the spirit of the invention. It is therefore intended that the appended claims cover all such equivalent variations as fall within the true spirit and scope of the invention.